THE
AMERICAN HEART JOURNAL

©Am. Ht. Assn.

VOLUME 21
JANUARY—JUNE, 1941

The American Heart Journal

Original Communications

CHANGES IN HEART VOLUME IN ADDISON'S DISEASE AND THEIR SIGNIFICANCE

THOMAS H. MCGAVACK, M.D.
NEW YORK, N. Y.

THE fact that the hearts of patients who die of Addison's disease are unusually small has attracted considerable attention.[1, 2, 3] On the other hand, there has been little or no comment upon the variations in the size of the heart which occur during life in any of the several stages of adrenal insufficiency. With the discovery and perfection of potent therapeutic agents, these changes should assume more than academic interest. Cardiac dilatation and pulmonary congestion have already been reported in two patients who were undergoing treatment with large doses of adrenocortical hormone.[4] The rapid retention of sodium and water in such patients may be but part of the explanation for the cardiac embarrassment.

The present observations suggest that chronic insufficiency of the adrenal cortex produces a diminution in the size of the heart which is directly related to a loss of cortical function. The further, sudden decrease which occurs when crisis supervenes appears to be the result of lowered blood volume, and disappears when dehydration is corrected.

METHODS AND MATERIALS

Six patients with Addison's disease formed the basis of the study.

Cardiac volume was estimated from the frontal and sagittal cardiac silhouettes according to the method of Rohrer[5] and Kahlstorf,[6] as modified by Comeau and White,[7] except that teleroentgenography was employed instead of orthodiascopy, and measurement of the frontal cardiac area was made by means of accurately ruled graph paper which contained subdivisions of 0.04 sq. cm. It is obvious that any method of calculating heart volume in vivo is faulty, not only because the heart fails to correspond accurately to any geometric figure, but also because the normal variations consequent upon body build are considerable.[8] The present observations are of comparative value in so far as multiple estimations in each of a series of patients are concerned.

Surface area was estimated by means of Boothby and Sandiford's nomogram.[9]

1

Blood volume was calculated by an adaptation of the Congo red method of Rowntree, Brown, and Roth.[2] While the factors of error, as suggested by Gibson and Evans,[10] make for inaccuracy in absolute values, all conditions of the estimations were standardized. The readings are therefore believed to be reliable for comparative purposes in the case of any one patient. Normal standards for blood volume were derived from the graph of Gibson and Evans,[10] which relates them to height (ht) or surface area (Sa), and from the tables of Rowntree, et al.,[2] which add a factor for "fullness index."

Serum sodium was estimated by the method of Hawk and Bergeim,[11] and serum potassium by that of Kramer and Tisdall as modified by Rappaport.[12] The daily intake of sodium and fluid was only approximated but is believed to be accurate within ±5 per cent.

Potent commercial extracts of adrenal cortex and synthetic adrenocortical hormone* were used throughout the study, as indicated.
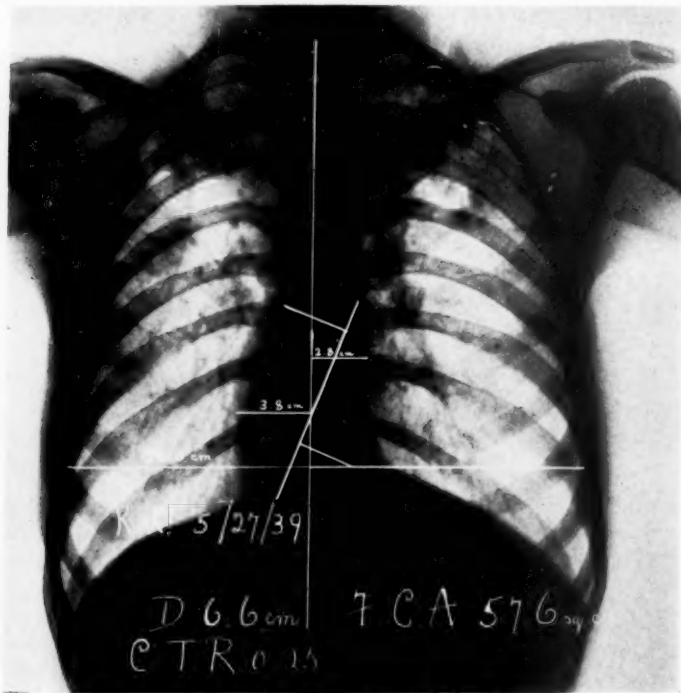
Fig. 1a.

Fig. 1.—Case 1: Roentgenograms of chest (a) during a crisis; (b) during period of cortical insufficiency, but after recovery from crisis; (c) when fully stabilized on synthetic cortical hormone. Note striking changes in size of the frontal cardiac area.

CASE REPORTS

CASE 1.—K. K., a 36-year-old Greek, whose illness had begun 1.5 years prior to admission to the hospital with anorexia, alternating periods of diarrhea and constipation, asthenia, pigmentation of the skin, and the loss of approximately 45 pounds of weight, for one month prior to admission had been bedridden as a result of weakness and entered the hospital in a crisis.

Fig. 1b.
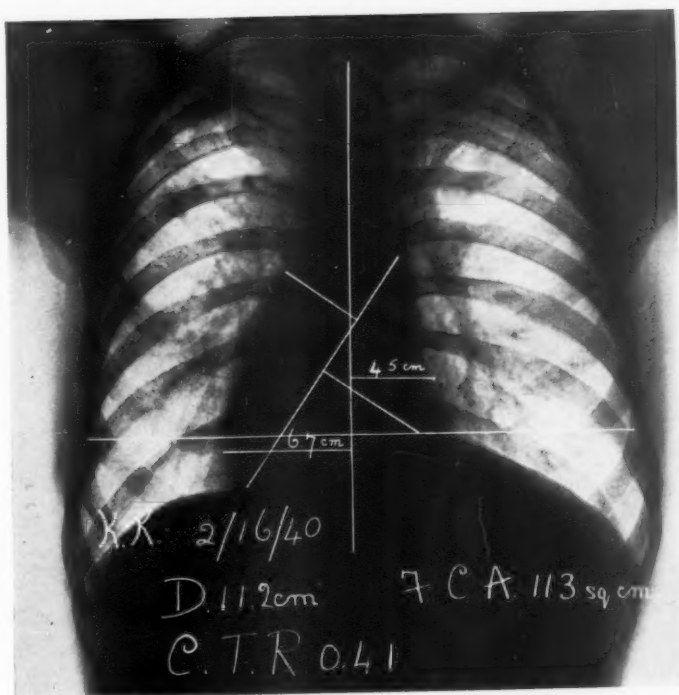
Fig. 1c.

He was a cold, drowsy, lethargic, well-developed, but emaciated, man who was 161 cm. tall and weighed 40 kg. There was deep, generalized pigmentation of the skin. Discrete areas of simila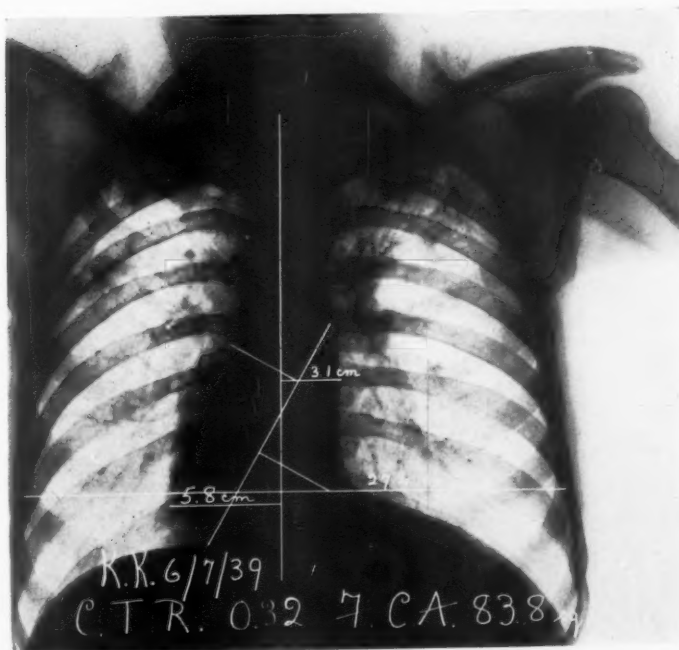r pigmentation were present on the buccal mucous membrane. The tongue was normal. At the apices of both lungs, bronchovesicular breathing and fine subcrepitant râles were heard. The cardiac borders were made out with difficulty; the heart sounds were distant and of poor quality. The blood pressure was 80/50.
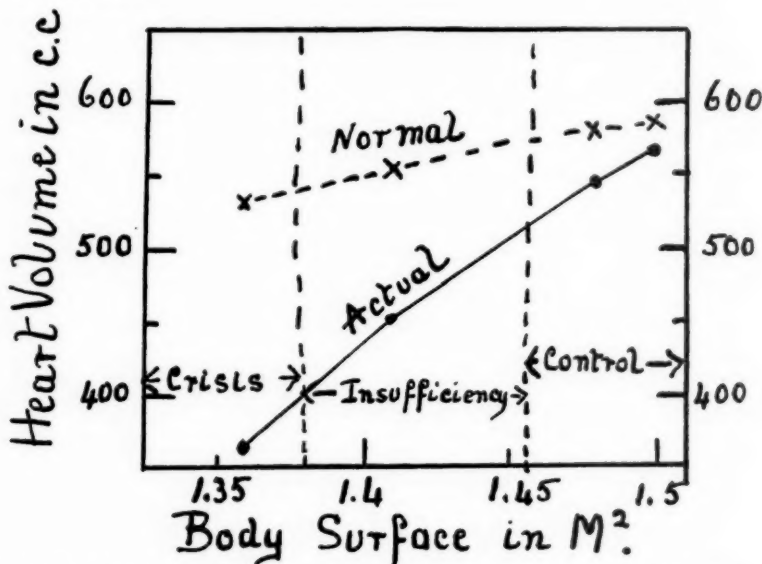
Chart I.—Relation of heart volume to body surface in various stages of Addison's disease (Case 1).
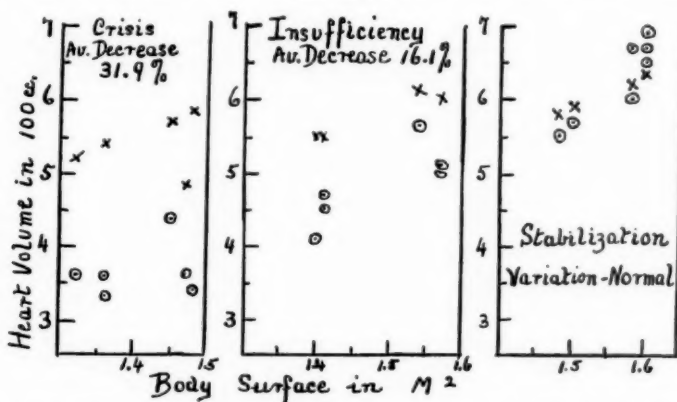
Chart II.—Relation of heart volume to body surface in various stages of Addison's disease. (× = Theoretic values. ⊙ = Actual values.)

Laboratory data (Table I) on admission. The urine showed a specific gravity of 1.018, a faint trace of albumin, many hyaline and granular casts, and an occasional, cuboidal, epithelial cell, but no blood or pus. The erythrocyte count was 4,360,000 per c.mm., the hemoglobin, 89 per cent, and the leucocyte count, 14,900 per c.mm.; the differential count showed, in per cent, polymorphonuclear cells, 67; eosinophiles, 3; lymphocytes, 28; and monocytes, 2. The total blood volume was 2,903 c.c. The

TABLE I

RELATION OF HEART SIZE, BLOOD VOLUME, BLOOD PRESSURE, AND ELECTROLYTE BALANCE IN VARIOUS STAGES OF ADDISON'S DISEASE

CASE 1

AGE 36 YEARS — HEIGHT 161 CM.

DAY OF OBS.	WT. (KG.)	B.P.	C.T.R.[a]	F.C.A.[b]	HEART VOL. PER KG.	HEART VOL. C.C./M2	TOTAL BLOOD VOL. (C.C.)		SERUM IN MG. %		DAILY INTAKE[d]		CLIN. CONDITION[f]
							ACTUAL	THEORETIC[c]	Na	K	Na (GM.)	HORMONE[e]	
1	40	80/50	0.25		7.1	208.1	2903	4268	260.0	25.3	11.0 K2.0	10 (E) 4 days	C.
11	41.8	96/50	0.32		9.9	296.2	4320	4501	265.5	10.3	11.0 K2.0	5 (E)	C. I.
30	42.7	104/70	0.38		9.2	277.4	4200	4517	279.0		No treatment three weeks		C. I.
51	40.0	74/50	0.26	74.2	9.3	263.6		4268	259.0		11.0 K2.0	0	I.C.
58	42.3	90/60	0.34	92.4	10.7	322.0			292.0		11.0 K2.0	5 (S)	C. I.
112	47.7	120/80	0.42	110.6	11.5	371.9		4755	341.0	14.0	11.0 K2.0	5 (S)	F. S.
154	50.0	140/80	0.39	101.8	10.2	337.8		4797	382.0	13.4	11.0 K2.0	5 (S)	F. S.
256	50.0	130/82	0.41	113.0	11.4	379.7	4730	4797	355.0	17.8	6.0	300 (I)	F. S.

(a) C.T.R., Cardiothoracic ratio

(b) F.C.A., Frontal cardiac area

(c) Rowntree, et al.[2]

(d) Represents daily intake or dose begun on date noted and continued to time of next observation.

(e) Glandular extracts (E) in c.c.
Synthetic hormone in mg.—oily suspension for injection (S)
—compressed tablet for implant (I)

(f) C, Crisis; I.C., impending crisis; C.I., cortical insufficiency; F.S., fully stabilized.

carbon dioxide combining power of the blood plasma was 52 volumes per cent. The
values for the blood chemical constituents, in milligrams per cent, were: (for the
plasma) nonprotein nitrogen, 54.3; urea nitrogen, 28.7; creatinine, 2.1; inorganic
phosphorus, 7.2; sugar, 69.0; and sugar after the ingestion of 100 Gm. of glucose
(readings at half-hour intervals), 92, 98, 106, 88, 65, 65; and, for the serum, chlorides
(as NaCl), 429; sodium, 260; and potassium, 25.3. The basal metabolic rate was
plus 0.5 per cent. Roentgenographic examination revealed a tuberculous infiltration
in the infraclavicular regions of both lungs, more extensive on the left side. The
heart was very small. Small, calcified areas were seen just above the right kidney,
in the region of the adrenal gland. The electrocardiogram showed a low T_1 and a
biphasic T_2 and T_3, with notching of the T in both chest leads.

The course of this patient can be followed by referring to Table I. The symptoms
and signs of crisis were relieved within four days. On the eleventh hospital day
the blood cell counts and nonprotein nitrogen content of the plasma were normal
and remained so thereafter. The patient's clinical improvement paralleled the changes
in weight, blood pressure, serum sodium, and so forth, as seen in Table I. Glucose
tolerance curves on the thirtieth, the fifty-eighth, the one hundred twelfth, and
the two hundred fifty-sixth days of observation varied little from the initial one;
there was a high tolerance in every instance.
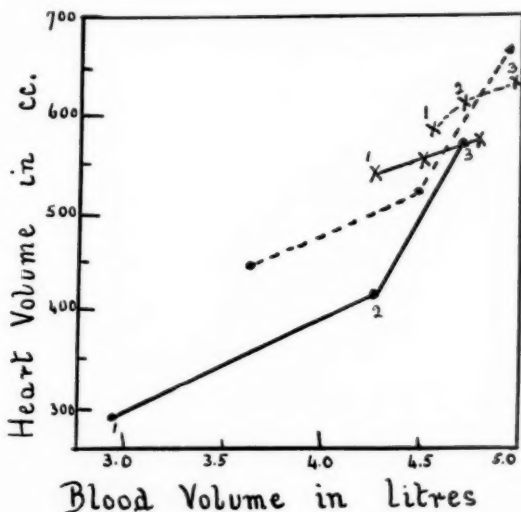
Chart III.—Relationship of heart volume to blood volume in Addison's disease as
compared with the normal. (————— = Case 1. -------- = Case 2. ● = Actual
values. ✕ = Theoretic "normal" values.)

At the present time, with subcutaneous implants of desoxycorticosterone totaling
300 mg., he is able to do half-time work without loss of weight or strength. The
changes in heart volume and their relation to body surface, to blood volume, to
various stages of the disease, and to the normal, are shown in Table I, Charts I, II,
and III, and in Fig. 1.

CASE 2.—G. V., a 24-year-old white Italian, was admitted to the hospital because
of bilateral, caseous, pneumonic tuberculosis, with a large cavity in the right upper
lobe. His infection had begun two years previously with a right-sided pleurisy.
At the time of admission he was a well-developed man with signs of disease in the
apices of both lungs. The heart was normal in size, shape, and position; the heart

TABLE II

Relation of Heart Size, Blood Volume, Blood Pressure, and Electrolyte Balance in Various Stages of Addison's Disease

AGE 24 YEARS   CASE 2   HEIGHT 153 CM.

DAY OF OBS.	WT. (KG.)	B.P.	C.T.R.[a]	F.C.A.[b]	HEART VOL. PER KG.	HEART VOL. C.C./M²	TOTAL BLOOD VOL. (C.C.)		SERUM IN MG. %		DAILY INTAKE[d]		CLIN. CONDITION[f]
							ACTUAL	THEORETIC[c]	Na	K	Na (GM.)	HORMONE[e]	
1	58.4	115/80	0.41	98.6	11.5	424.7					Ward diet		
152	60.2	118/80	0.39	88.0	9.9	378.9					Ward diet		
195	59.8	96/66	0.36	95.0	10.5	402.8					Ward diet		C. I.
239	58.0	88/70	0.34	85.8	9.8	368.5	4520	4776	308.0	22.4	11.5	0	C. I.
291	50.0	78/50	0.31	72.5	9.2	321.3	3080	4555	290.0	31.7	15.0	0	I. C.

Symbols (see Table I).

rate was 85; the blood pressure was 115/80; the cardiac mechanism was normal; the pulmonic second sound was accentuated; and no murmurs were heard.

Among the laboratory data were an erythrocyte count of 3,550,000, a hemoglobin value of 80 per cent, and a leucocyte count of 11,600, with a normal differential count. The urine was normal. The sputum gave a Gaffkey 4 reaction for tubercle bacilli. The blood sugar was 110 mg. per cent, and the total nonprotein nitrogen, 33.7 mg. per cent.

The patient's condition improved slightly during the first 150 days of hospitalization. He gained two kilograms in weight, and there was some clearing of the lesions in the apices. On the one hundred ninety-fifth day of observation his blood pressure had dropped to 96/66, and there was a questionable change in skin coloration, but no alteration in the volume of the heart could be detected (Table II). Thereafter, he grew steadily worse. On the two hundred thirty-ninth day he had all of the manifestations of adrenal cortical insufficiency (Table II), with a diminution in heart volume, a serum potassium of 22.7 mg. per cent, and a serum sodium of 308.0 mg. per cent, but his blood volume was normal (4,520 c.c.). Forty-five days later he had a crisis, with still further lowering of his blood pressure (78/50), blood sodium, and cardiac volume, an elevation of serum potassium to 31.7 mg. per cent, and a total blood volume of only 3,680 c.c. (Table II). He died of adrenal cortical insufficiency on the three hundred sixteenth day of observation.

CASE 3.—E. M. was a 53-year-old, well-developed and well-nourished German woman. She had had a cholecystotomy because of cholelithiasis at the age of 38, a cholecystectomy because of cholelithiasis at the age of 50, scanty, irregular menses, and had passed the menopause at the age of 48. She had first noticed pigmentation of the skin three years previously. During the preceding six months this had become progressively worse and had been associated with loss of weight (approximately 20 pounds), gradually increasing anorexia, asthenia, abdominal pain, vomiting, and diarrhea.

The most remarkable thing about the patient was a generalized pigmentation of the entire body, the tongue, and the buccal mucous membrane. The fingernails and toenails showed a very deep purplish-black color which varied considerably in intensity from day to day. The heart sounds were of poor quality. The blood pressure was 96/60. She weighed 58.2 kg. and was 145 cm. tall.

Repeated urinalyses were negative; there was no hematoporphyrinuria, hemoglobinuria, hemosiderinuria, or urobilinuria. The icteric index was 6. There was a mild secondary anemia. The basal metabolic rate was plus 6. The Mantoux reaction was positive. The serum proteins were normal. The values for the other blood chemical constituents, in milligrams per cent, were: nonprotein nitrogen, 28.0; urea nitrogen, 11; creatinine, 1.4; sugar, 88; serum sodium, 276; serum potassium, 20; serum chlorides (as NaCl), 410; calcium, 10; inorganic phosphorus, 3.75; cholesterol, 125; cholesterol esters, 52.5. These remained approximately the same on repeated examinations, with the exception of the sodium, potassium, and chloride values, which, three days prior to death, on the seventy-fifth day, were 367, 8.7, and 562, respectively.

The electrocardiogram and roentgenograms of the lungs, abdomen, and skull were essentially normal. The heart was small. Its transverse diameter was 10.4 cm.; the cardiothoracic ratio was 0.42; and the heart volume was 228 c.c. per square meter of body surface.

The patient was given approximately 12 Gm. of sodium and 10 to 40 c.c. of adrenal cortical extract daily. Temporary improvement followed, but after two weeks on a diet which contained approximately normal amounts of sodium a sudden relapse occurred, and the patient died in twenty-four hours, despite the administration of 18 Gm. of sodium and 50 c.c. of cortical extract.

Autopsy.—The heart weighed 195 Gm. The left adrenal was small, atrophic, and flat; it weighed 2 Gm. The right adrenal was almost completely destroyed by a hemorrhage which had been caused by thrombosis of the artery.

CASE 4.—N. R., a 41-year-old, asthenic, emaciated, white woman, had been losing weight gradually for one year; she had also had weakness, cutaneous pigmentation, and nausea, of increasing degree. For five days prior to admission she had been confined to bed because of weakness, nausea, and diarrhea. When she was admitted, she was in shock, was mildly disoriented, and was "too weak to raise her head." There was a brownish pigmentation of the skin of the hands and face, and, to a less marked degree, of that of the trunk. The heart was small and the sounds distant. The blood pressure was 76/40. She weighed approximately 45.4 kg. and was 163 cm. tall.

The urinalysis was negative. There was hemoconcentration, with a moderate leucocytosis. The nonprotein nitrogen content of the blood was 46 mg. per cent, and the serum sodium was 240.1 mg. per cent. Roentgenograms of the chest revealed inactive, bilateral apical tuberculosis and a small heart. The transverse diameter of the heart was 7.4 cm.; the cardiothoracic ratio was 0.30; and the heart volume was 245 c.c. per square meter of body surface.

Improvement followed a high intake of sodium (15 Gm. daily) and fluid (3,500 c.c. daily). On the third day the patient's family took her home, and attempts to follow her course have failed.

CASE 5.—W. P., a 46-year-old, emaciated, white woman, was admitted to the hospital in a state of shock, with a history that her illness had begun with seasickness six months previously. Nausea, weakness, anorexia, diarrhea, and dyspnea had appeared in the order named. Physical examination revealed circumscribed areas of pigmentation over the entire body and the buccal mucous membrane. The heart sounds were feeble, but there were no murmurs. The blood pressure was 120/60. Three days later her weight was 38.6 kg., and her height, 157 cm. The erythrocyte count was 4,800,000; the hemoglobin, 97 per cent; and the leucocyte count, 12,600. The serum sodium was 266 mg. per cent. The transverse diameter of the heart was 9.5 cm.; the cardiothoracic ratio, 0.39; and the cardiac volume, 271.9 c.c. per kilogram of body weight. The electrocardiogram showed a high normal P-R interval (0.20 sec.), small and slightly slurred QRS complexes, and low T waves in all leads. As a result of the daily administration of 2,000 to 3,500 c.c. of fluid, 15 Gm. of sodium, and 10 to 30 c.c. of cortical extract parenterally, the patient's condition was markedly improved, and she was discharged on the thirty-fifth day.

CASE 6.—E. M., a 42-year-old, emaciated Irishman, who was admitted to the hospital during an impending crisis, had developed, over a period of two years, weakness, pigmentation of the hands, face, and genitalia, loss of weight, and attacks of nausea and vomiting, all of which were steadily increasing in severity. On admission he complained of upper abdominal pain which was so severe as to suggest the presence of an acute surgical condition.

He weighed 52.7 kg., was 165 cm. tall, and showed irregular pigmentation of the entire body surface, but no mucous membrane lesions. His lungs appeared to be normal; the heart was small; and the blood pressure was 66/55. The upper abdomen was tender and slightly rigid; the temperature was subnormal. The urine was negative except for a trace of albumin. The erythrocyte count was 5,000,000; the hemoglobin, 100 per cent; and the leucocyte count, 19,200, with a normal differential count. The values for the blood chemical constituents, in milligrams per cent, were: (for the plasma) nonprotein nitrogen, 46; sugar, 91; and sugar after the ingestion of 100 Gm. of glucose (readings at half-hour intervals), 91, 92, 115, 82, 73, 80; and (for the serum) sodium, 288; potassium, 25.9; and chlorides (as NaCl), 420. A frac-
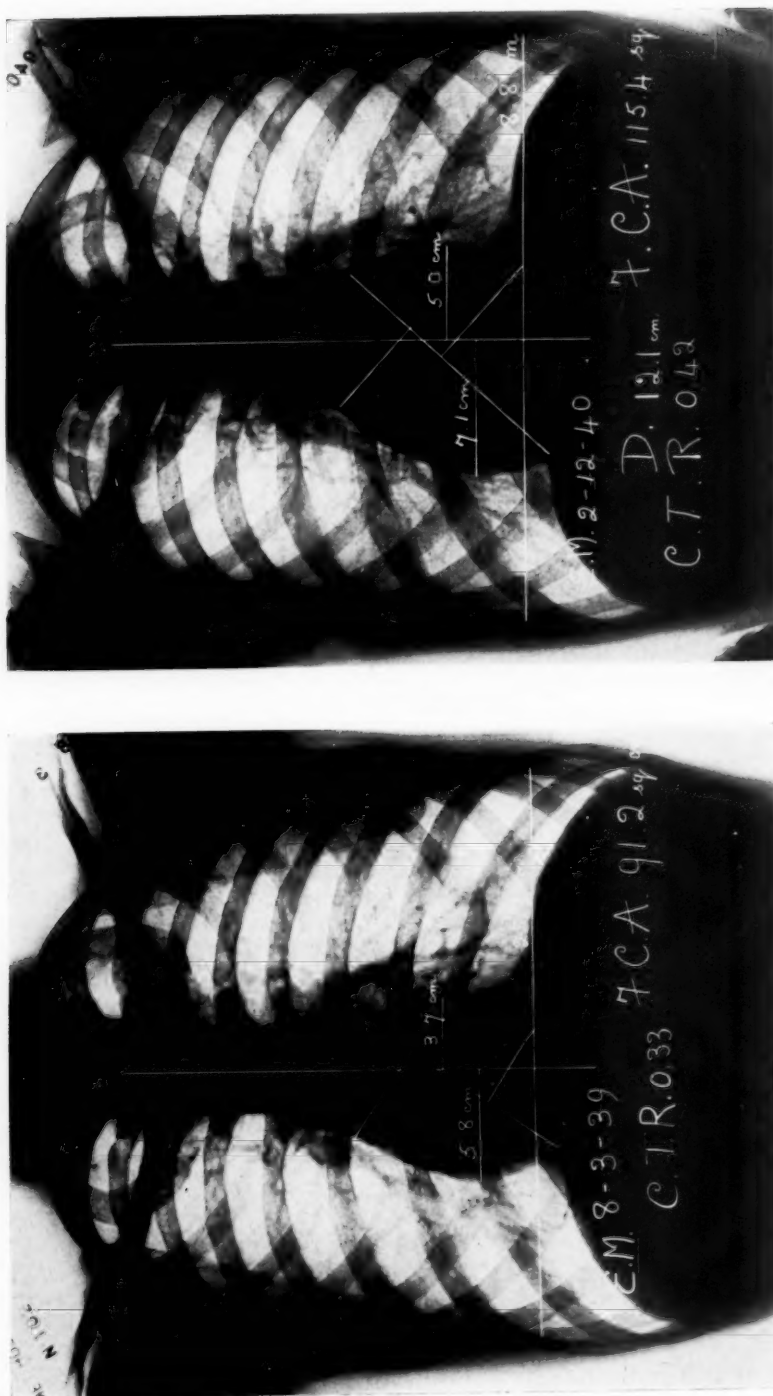
Fig. 2a.

Fig. 2b.

Fig. 2.—Case 6: Roentgenograms of chest (a) during cortical insufficiency; (b) after full stabilization on desoxycorticosterone.

TABLE III

RELATION OF HEART SIZE, BLOOD VOLUME, BLOOD PRESSURE, AND ELECTROLYTE BALANCE IN VARIOUS STAGES OF ADDISON'S DISEASE

AGE 42 YEARS   CASE 6   HEIGHT 165 CM.

DAY OF OBS.	WT. (KG.)	B.P.	C.T.R.[a]	F.C.A.[b]	HEART VOL. PER KG.	HEART VOL. C.C./M2	TOTAL BLOOD VOL. (C.C.)		SERUM IN MG, %		DAILY INTAKE[d]		CLIN. CONDITION[f]
							ACTUAL	THEORETIC[c]	Na	K	Na (GM.)	HORMONE[e]	
2	52.7	66/55	0.33	91.6	9.8	330.8			288.0	25.9	12.0 K2.0	2.5 (E)	I.C.
9	52.7	80/50	0.33	91.2	9.8	329.3			275.7		12.0 K2.0	10 (E)	I.C.
36	53.1	95/75	0.45	118.8	11.0	372.6			350.0	25.1	12.0 K2.0	10 (S)	C.I.
55	53.6	130/70	0.46	110.4	12.0	413.8			448.0	12.4	6.0	7.5 (S)	F.S.
143	55.4	140/90	0.46	118.8	12.8	444.3			314.0	13.9	6.0	5.0 (S)	F.S.
198	53.8	124/80	0.42	115.4	12.8	437.0			308.0	20.2	6.0	5.0 (S)	F.S.

Symbols (see Table I).

tional gastric analysis showed nothing abnormal. The basal metabolic rate was minus 10 per cent. Roentgenologic examination disclosed discrete, calcified, healed, tuberculous foci in the apices of both lungs. The heart shadow was small; its transverse diameter was 9.3 cm. The cardiothoracic ratio was 0.33; and the heart volume was 330 c.c. per square meter of body surface (Fig. 2). In all leads of the electrocardiogram there were slurring of the R wave and low amplitude of the T waves. Subsequent blood cell counts and glucose tolerance curves showed little change. When the patient was fully stabilized, the plasma volume was 3,692 c.c. and the total blood volume was 4,995 c.c.

The patient was given 12.0 Gm. of sodium and 10 to 30 c.c. of adrenal cortical extract daily. His subsequent course can best be followed by referring to Table III and Fig. 2. The size of the heart increased slowly during the first four weeks but was not restored to normal until the patient was given desoxycorticosterone acetate (7.5 mg. daily). On the one hundred seventeenth day of observation two tablets of desoxycorticosterone, each weighing 150 mg., were implanted subcutaneously. Thereafter it was possible to discontinue all injections, except for a short febrile period when supplemental injections of 5 mg. of the drug, in oil, were given daily.

DISCUSSION

The transverse diameter of the heart was below normal limits in each patient who showed signs of cortical insufficiency and was most strikingly altered during crises. In contrast to the "horizontal depth diameter," which varied but little from time to time in any individual patient, the transverse measurement underwent wide fluctuations which roughly paralleled the severity of the Addison's disease.

The cardiothoracic ratio, that is, the transverse diameter of the heart divided by the transverse diameter of the thorax, afforded an even more accurate index of the seriousness of the disease.

With the exception of Case 3, the measurements in which were made when a crisis was impending, a cardiothoracic ratio below 0.40 invariably represented cortical insufficiency, and ratios below 0.32 occurred only during crises. When adequate treatment for the adrenal deficiency was instituted, as, for instance, in Cases 1 and 6, the ratios ranged from 0.41 to 0.46. The estimation of cardiothoracic ratios from serial teleroentgenograms suggests itself as a logical method of following the effects of therapy in Addison's disease, except in cases in which the chest is unusually flat or deep, as noted by Liljestrand, et al.[13] Our Case 3 was an instance of this type of thorax; the patient had a normal cardiothoracic ratio but a markedly reduced heart volume per kilogram of body weight (5.8 c.c.).

In any individual chest, however, cardiac volume is a reasonably constant function of the "frontal cardiac area." In no instance did the frontal cardiac area of a patient in crisis exceed 77.0 sq. cm., and in but one such instance was the cardiac volume per square meter of body surface above 300 c.c. (302.4 c.c.) The difficulty which is encountered in obtaining absolute values for the volume of the heart in the living subject has already been stressed.[7] It has been found that there is a linear correlation between heart volume and body weight or body surface.

Comeau and White,[7] after a study of 170 normal persons, state that "this correlation, however, was not sufficiently close to allow the derivation of a reliable index as a criterion for normal." The same problem is inherent in the work of Liljestrand, et al.,[13] who, however, estimated an average mean heart volume for each of two groups of men whom they studied. This mean figure has been used for the determination of the theoretically normal heart volume in our charts. Although we recognize the fallacies of such a method, the differences in the various stages of adrenal insufficiency seem to be so marked as to offer little room for controversy. From examination of Charts I and II, it is clear that heart volume is disproportionately reduced in relation to surface area in patients with adrenal insufficiency. In five cases, during crises, the average reduction amounted to 31.9 per cent (Chart II), whereas it was 16.1 per cent in three persons with adrenal insufficiency who were not having crises. The heart volume was normal in Patient 2 before the development of Addison's disease, and attained normal proportions in Patients 1 and 6 after adequate hormonal therapy.

The relation of these changes in heart volume to alterations in total blood volume in Cases 1 and 2 is shown in Chart III. Significant blood volume changes seem to occur only during crises and are the result of sodium and water loss from the body. These alterations, chiefly, if not wholly, in the plasma and tissues,[14] account for a definite portion, but not for all, of the variations in heart volume that we observe in Addison's disease. Blood volume can be restored to normal by the administration of sufficiently large quantities of water and salt, but heart volume returns to normal only when adequate amounts of adrenocortical hormone are also supplied (Chart III). This would suggest that the adrenal cortex has a definite effect upon heart size, a fact which is borne out by studies of autopsy material.[1, 15] Moreover, recent experimental work on rats[16] has shown that thymic hyperplasia and splanchnomicria follow adrenalectomy, whereas thymic atrophy and splanchnomegaly are produced by the administration of either the adrenotropic hormone of the pituitary or adrenocortical hormone.

It may be contended by some that this disproportionate decrease in heart size is the result of simple inanition, or "starvation." However, in guinea pigs, prolonged starvation has little effect upon "the normal heart weight/body weight ratio."[17] Again, the weights of the atrophic hearts of rats which were suffering from thirst, starvation, and vitamin B deficiency showed the same ratio to body weight as the heart weights of normal animals of the same size.[18] Lusk[19] quotes Voit's very early observations on the starved cat, which confirm the above observations and even suggest that the decrease in cardiac weight may be disporportionately small. Finally, Smith,[20] in a study upon human beings, states that "there is a definite correlation between the weight of the heart and the weight of the body. . . . The ratio is slightly higher in thin persons."

Estimations of heart volume may eventually prove to be of value in calculating optimum dosage of adrenocortical hormones. Until recently, overdosage was virtually impossible, for sufficiently potent materials were not available. With the advent of synthetic material, notably desoxycorticosterone, and the prospect of obtaining an extract of the cortex itself which is believed to be 100 times as effective as the present synthetic material,[21] the possibility of overdosage has become real.[4] Ferrebee and his associates[4] noted edema of varying degree in ten of thirteen patients treated. Three patients developed respiratory distress, with roentgenologic evidence of pulmonary congestion, and in two of them serious cardiac insufficiency, with dilatation, was observed. Following prompt therapy one recovered, but the other died of a complicating pneumonia. We have not seen these complications, but our dosages of hormone have not been as large as those originally used by the above-mentioned workers. In an addendum to their communication, they state that this complication can be avoided by using smaller doses of hormone and not giving more than the usual amount of salt in the diet.

In Cases 1, 3, and 6, it will be noted that high sodium values were maintained in the blood during periods of stabilization as long as the sodium intake was held at a high level (approximately 12.0 Gm. daily). These diminished promptly in Cases 1 and 6 when a general ward diet, containing approximately 6.0 Gm. of sodium, was resumed. It was thought at first that the point of hormonal tolerance could be determined by blood sodium levels and glucose tolerance tests. The experiences mentioned above, and those of Ferrebee and his associates,[4] have shown the dangers which are inherent in using sodium estimations as a sole criterion of optimal dosage. Glucose tolerance curves were influenced but little by the synthetic hormone (Cases 1 and 6) in doses which, nevertheless, appeared to contain ample amounts of the "vital factor." Wells and Kendall[22] found that retention of sodium and a depression of potassium to low levels resulted from the use of desoxycorticosterone and its acetate. The depression of potassium was evident in all of our cases, but the rise of sodium to high levels occurred only under desoxycorticosterone treatment when the intake of sodium was concomitantly high, viz., 12 or more Gm. daily. Is it possible that the cortical hormone is even more complex than was suggested by the work of Hartman and his associates,[23] who succeeded in separating a "vital" and a "sodium regulating" fraction? Inasmuch as blood sodium values may be readily influenced by salt ingestion, and blood glucose levels remain low despite therapy, it may be profitable to turn to a study of teleroentgenograms, together with blood pressure and weight changes, as safe methods for ascertaining the optimal procedure in the management of the patient with Addison's disease. When transverse cardiac diameter, cardiothoracic ratio, and heart volume have been

restored to normal the dosage should be curtailed to a point at which a general sense of well-being is maintained, and a gradual gain in weight and strength is attained.

SUMMARY

1. In six cases of Addison's disease the relationship between cardiac mensuration and the stage of the disease was studied.

2. An average reduction in heart volume of 31.9 per cent was observed in five instances of crisis, and of 16.1 per cent in three patients with cortical insufficiency who were not having crises.

3. Prior to the development of Addison's disease, one patient had a cardiac volume which was within normal limits. Two others who were first observed during a crisis, and with a crisis impending, respectively, regained a normal heart volume when they were adequately treated.

4. Serial estimations of blood volume were carried out upon two patients. Significant lowering was seen only during crises. Values within the normal range were noted in patients with cortical insufficiency who were not having crises.

CONCLUSION

The reduction in cardiac volume observed in Addison's disease is a direct effect of the inadequate supply of adrenocortical hormone. When crisis supervenes, the diminished blood volume plays a striking accessory role in still further decreasing the size of the heart.

REFERENCES

1. Barker, N. W.: The Pathological Anatomy in 28 Cases of Addison's Disease, Arch. Path. **8:** 432, 1929.
2. Rowntree, L. G., Brown, G. E., and Roth, G. M.: The Volume of the Blood and Plasma in Health and Disease, Philadelphia, 1929, W. B. Saunders Co.
3. Grollman, A.: The Adrenals, Baltimore, 1936, Williams & Wilkins Co.
4. Ferrebee, J. W., et al.: Desoxycorticosterone Esters; Certain Effects in the Treatment of Addison's Disease, J. A. M. A. **113:** 1725, 1939.
5. Rohrer, F.: Volumbestimmung von Körperhöhlen und Organen auf orthodiagraphischem Wege, Fortschr. a. d. Geb. d. Röntgenstrahlen **24:** 285, 1916-17.
6. Kahlstorf, A.: Über eine orthodiagraphische Herzvolumenbestimmung, Fortschr. a. d. Geb. d. Röntgenstrahlen **45:** 123, 1932.
7. Comeau, W. J., and White, P. D.: An Evaluation of Heart Volume Determinations by the Rohrer-Kahlstorf Formula as a Clinical Method of Measuring Heart Size, AM. HEART J. **17:** 158, 1939.
8. Comeau, W. J., and White, P. D.: Body Build and Heart Size, AM. HEART J. **17:** 616, 1939.
9. Boothby, W. M., and Sandiford, R. B.: Nomographic Charts for Metabolic Rate Determinations, Am. J. Physiol. **55:** 296, 1921.
10. Gibson, J. G., 2nd, and Evans, W. A., Jr.: Clinical Studies of the Blood Volume, J. Clin. Investigation **16:** 301, 317, 851, 1937.
11. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, ed. 11, Philadelphia, 1937, P. Blakiston's Son & Co.
12. Rappaport, F.: Methodisches zur Bestimmung der Chloride des Kaliums und des Calciums im Blute, Klin. Wchnschr. **12:** 1774, 1933.

13. Liljestrand, G., et al.:   Normal Heart Volume in Man, AM. HEART J. 17: 406, 1939.
14. Harrop, G. A., et al.:   Studies on the Suprarenal Cortex.   II. Metabolism, Circulation, and Blood Concentration During Suprarenal Insufficiency in the Dog, J. Exper. Med. 58: 1, 1933.
15. Rowntree, L. G., and Snell, A. M.:   A Clinical Study of Addison's Disease, Philadelphia, 1931, W. B. Saunders Co.
16. Crede, R. H., and Moon, H. D.:   Effect of Adrenocorticotropic Hormone on Thymus of Rats, Proc. Soc. Exper. Biol. & Med. 43: 44, 1940.
17. Van Liere, E. J., and Sleeth, C. K.:   The Effect of Prolonged Inanition on the Heart Weight/Body Weight (HW/BW) Ratio in the Mammal, Am. J. Physiol. 116: 635, 1936.
18. Sah, P. P. T., and Li, T. W.:   Effects of Thirst, Starvation, and Vitamin B Deficiency on the Weight of Internal Organs, Chinese J. Physiol. 4: 255, 1930.
19. Lusk, G.:   The Elements of the Science of Nutrition, ed. 4, Philadelphia, 1928, W. B. Saunders Co., p. 112.
20. Smith, H. L.:   The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, AM. HEART J. 4: 79, 1928.
21. Grollman, A.:   The Comparative Activity of Desoxycorticosterone and Other Crystalline Derivatives and of Purified Extracts of the Adrenal Cortex, J. Pharmacol. & Exper. Therap. 67: 257, 1939.
22. Wells, B. B., and Kendall, E. C.:   A Qualitative Difference in the Effect of Compounds Separated From the Adrenal Cortex on Distribution of Electrolytes and on Atrophy of the Adrenal and Thymus Glands of Rats, Proc. Staff Meet., Mayo Clin. 15: 133, 1940.
23. Hartman, F. A., Spoor, H. J., and Lewis, L. A.:   The Sodium Factor of the Adrenal, Science 89: 204, 1939.

THE USE OF THE CATHODE RAY FOR RECORDING HEART SOUNDS AND VIBRATIONS

II. Studies on the Muscular Element of the First Heart Sound

John R. Smith, M.D., Arthur S. Gilson, Ph.D., and
William B. Kountz, M.D.
St. Louis, Mo.

OVER a period of many years a multitude of experiments have been focused on the cause of the heart sounds and on various cardiac and circulatory conditions that influence them. The work has been fraught with difficulties, one of the greatest of which obviously lay in experimentation on the heart itself. Many ingenious experiments were devised with the object of studying the movements of the heart valves and how those movements produce or influence the heart sounds. Other experimental work aimed at silencing the valves, so that, if sounds are produced by the contracting myocardium, they could be detected and studied. Another difficulty appears to have been with the recording instruments which were employed. The earlier devices for registering the heart sounds graphically were crude. In recent years many refinements have been made in these methods, and the introduction of electric stethographs has marked a distinct advance. Most of the stethographs, however, are so designed that they record only the higher frequencies of the audible normal or adventitious sounds, or fail to record vibrations of too low an intensity to be heard.[1] By these means, however, much valuable information has been obtained.

It is now generally believed that the second heart sound is produced by the closure of the aortic and pulmonary semilunar waves. The cause of the first heart sound, however, is still a moot question. The statement is commonly made in standard textbooks (as pointed out by Dock[2]) that the first heart sound is composed of muscular and valvular "elements", although usually there are no discussions as to the nature of those respective elements. Many workers have clung to the belief that muscular components are present in the first sound,[3, 4, 5, 6] but have emphasized the role of the auriculoventricular valves in producing and modifying it. More recently, Dock[2] was led to the conclusion that the contracting myocardium plays no part in the causation of the first heart sounds, and that closure and tensing of the auriculoventricular valve leaflets are entirely responsible for the audible vibrations during normal ventricular systole.

We have reinvestigated the problem, with the hope of throwing more light on the components of the first heart sound. In a preliminary report, a general outline of the work was presented.[7]

17

METHOD

These experiments depend upon the immobilization of the auriculoventricular valves in such a way that the myocardium is permitted some latitude of contraction, so that the vibrations produced by the heart muscle alone can be detected and studied. The experiments were accomplished by the following method:

In each case the dog was anesthetized with veterinary nembutal. The thorax was opened by a midsternal incision, and respiration was maintained by a respiratory pump. The superior and inferior venae cavae were isolated (the azygos vein was completely ligated), so that rubber-padded clamps could be applied to the vessels to prevent any flow of blood to the heart. Small balloons, affixed to brass tubes 3 mm. in diameter, were introduced into the ventricular cavities by passing them through small incisions in the auricular appendages and pushing them through the auriculoventricular ostia. The balloons were so small when deflated that they did not interfere with cardiac function. The pericardium was left intact but was fastened to the diaphragm in order to prevent random movements of the heart; care was taken to avoid stretching the membrane and impairing normal cardiac movement. A few micrograms of barium chloride in saline were usually administered intravenously in order to decrease the likelihood of ventricular fibrillation as a result of the manipulation.

The heart sounds were recorded by means of a cathode-ray "vibrocardiograph." The instrument registers the wide range of vibrations produced by the heartbeat, some of which are of high enough frequency and intensity to comprise the heart sounds; the remainder are of low frequency and are not appreciated by the human ear. A description of the device and of the character of the cardiac vibrations registered by this method has been presented,[1] and need not be repeated here. In these experiments, the microphone of the vibrocardiograph was placed directly on the heart at the intraventricular septum, just above the apex. In order to prevent jarring of the microphone case, which would introduce artifacts into the curves, the instrument was suspended by rubber straps from a frame over the thorax, allowing the microphone button to rest firmly on the heart. The intact pericardium prevented friction between the receiver and the moving myocardium. Lead II of the electrocardiogram was obtained by embedding copper electrodes in the shoulder and thigh muscles. The paper speeds of the electrocardiograph and stethograph were matched, and the two records were synchronized by flashing lamps (flashing signals, occurring at intervals of 0.2 second) which played on the records simultaneously. A pair of crystal earphones which was connected to the amplifier of the stethograph permitted simultaneous auscultation of the heart. The latter auscultatory observations could be supplemented by placing the bell of an ordinary stethoscope on the ventricles.

The venae cavae were then clamped, and the "intraventricular" balloons carefully inflated with water or air to pressures of 50 to 70 mm. of mercury. These pressures distended the ventricles to approximately the normal diastolic size, and the balloons exerted sufficient pressure against the auriculoventricular valves to immobilize them and prevent change of tension in the valve membranes during systole. This was confirmed by experiments on hearts immediately after death, in which it was found that pressures of 50 mm. Hg in the balloons were more than adequate to render every part of the auriculoventricular valves quite inactive. The resilience of the balloons and the mobility of the manometric system permitted some degree of ventricular contraction against pressures more comparable to normal.

In addition, the experiments performed by Dock[2] were repeated. The heart vibrations were studied when the venae cavae were clamped and when the heart was contracting "isometrically." In the latter case, a ligature was passed around the auriculoventricular groove to prevent any blood flow to or from the ventricles. The
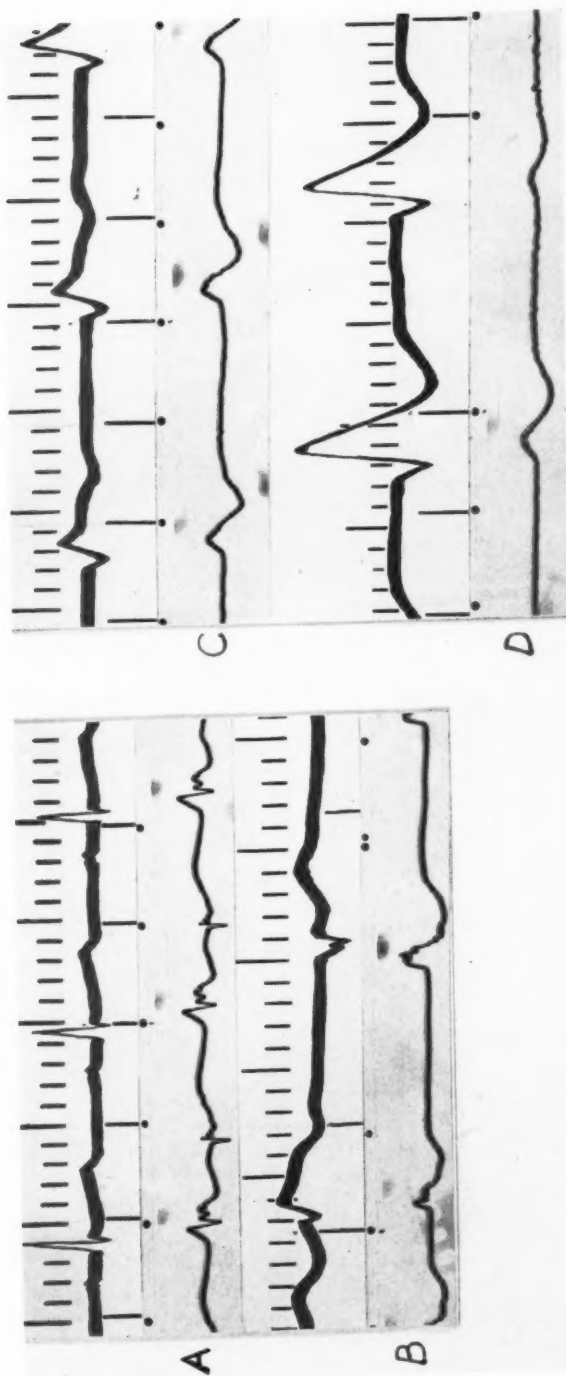
Fig. 1.—Electrocardiographic and vibrocardiographic curves obtained before and during inflation of balloons placed within the ventricular cavities (see text). The curves of the two instruments were synchronized by flashing lamps at intervals of 0.2 second. Since the paper speeds were not exactly the same, the flashing signals were occasionally interrupted, so that exactly synchronous points on each record could be determined, from which subsequent events in each could be measured. In this illustration, the electrocardiographic curve has been retouched to permit better reproduction.

normal functioning of the atrioventricular valves was abolished by the lack of
intraventricular pressure change in the former instance, and by the cord about the
A-V groove in the case of the "isometrically" contracting heart.

RESULTS

Following clamping of the venae cavae and inflation of the intra-
ventricular balloons, the first heart sound persisted until severe myo-
cardial failure supervened. The train of events will best be understood
by examination of the curves. Fig. 1 illustrates a typical experiment
from this series. Fig. 1A is a control curve obtained with the micro-
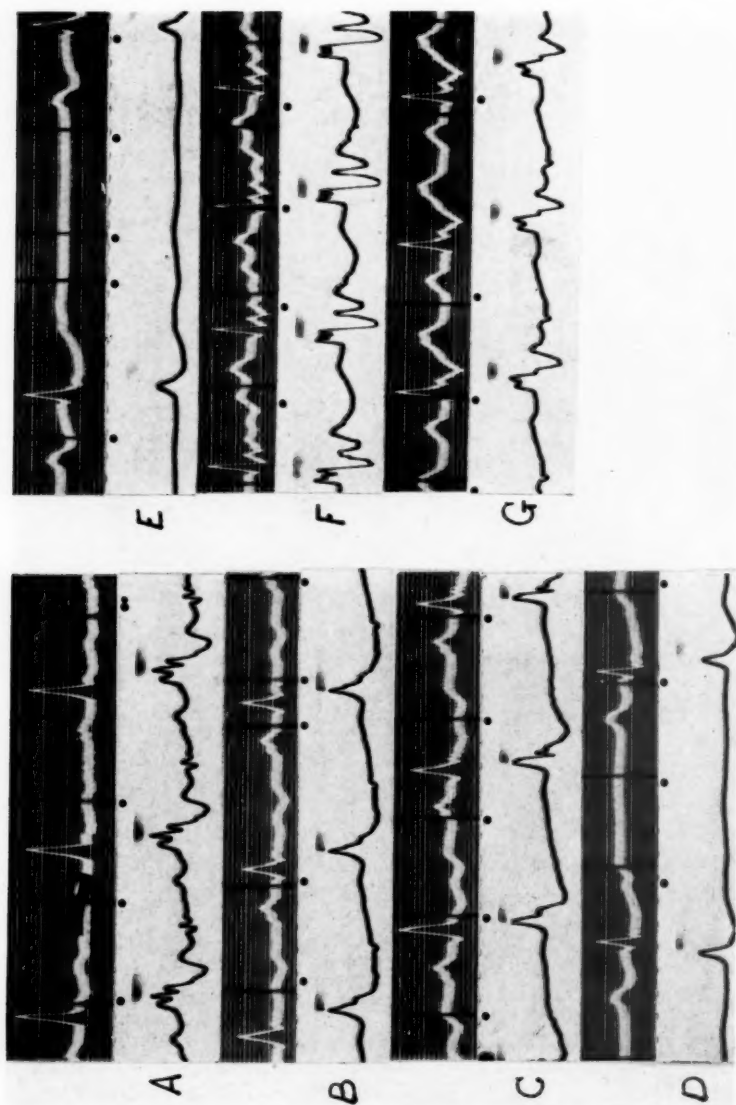phone resting directly on the heart, before the venae cavae were clamped

Fig. 2.—Curves obtained before, during, and after clamping of the superior and inferior venae cavae (see text).
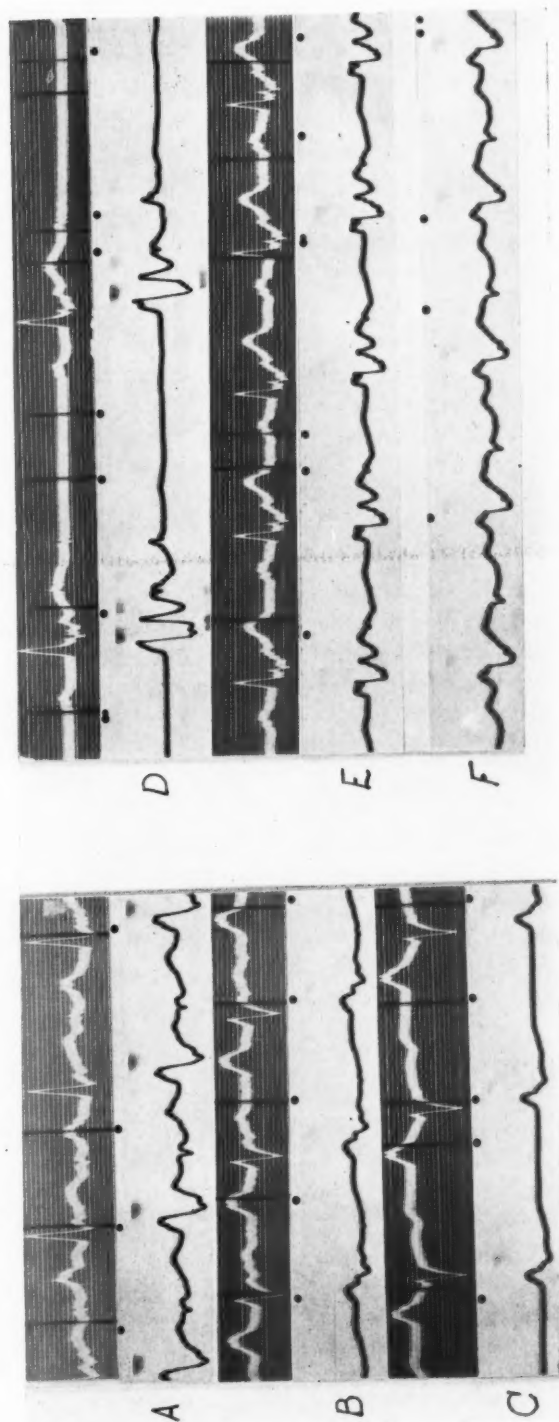
Fig. 3.—Electrocardiographic and vibrocardiographic curves obtained from the "isometrically" beating heart (see text).

and the balloons inflated. Fig. 1*B* is the tracing obtained immediately following inflation of the ventricular balloons. The second heart sound has disappeared, and the first vibration complex has become markedly altered. On auscultation, the first sound was dull and snapping in character. Figs. 1*C* and 1*D*, recorded two and four minutes, respectively, after inflating the balloons, show a persistence of vibrations synchronous with systole. Auscultation at these times revealed that the first sound became fainter as myocardial failure advanced, but it was snapping and dull in character. Almost immediately thereafter, ventricular fibrillation occurred.

Clamping of the superior and inferior venae cavae (Fig. 2) produced curves and auscultatory changes similar to those which resulted from inflation of the ventricular balloons. Fig. 2*A* was obtained from the normally beating heart before the experiment was begun. Curves *B*, *C*, and *D* were obtained immediately, one minute, and one and one-half minutes, respectively, after clamping the great veins; *E* was taken a few seconds following release of the vessels, two minutes after they had been unclamped, and *F* and *G* show a gradual return of the vibration complexes toward normal. Almost immediately after cutting off the venous flow the second heart sound disappeared. Auscultation during the period of clamping showed that the first sound was of a dull character; it became progressively more faint as the heart failed. It was seldom possible to occlude the venae cavae for more than two minutes at a time without precipitating ventricular fibrillation; however, until complete failure supervened, each systolic effort was accompanied by a sound of the character noted before.

The curves obtained after ligation of the auriculoventricular ostium, producing an ''isometrically'' contracting heart, are shown in Fig. 3. *A* is a control record. *B* and *C* illustrate the first vibration complex immediately, and one minute, respectively, following constriction. Auscultation revealed dull, distant sounds which were synchronous with systole. *D*, *E*, and *F* show a gradual return toward normal after release of the ligature.

In these three types of experiment the character of the sounds and the shape of the recorded vibrations bore striking resemblances to one another. In each case an audible first sound persisted until complete failure or ventricular fibrillation occurred. Occasionally, the shock incident to thoracotomy or other manipulation so affected the heart that it became weak or went into a state of failure before the experiments were begun. In such instances, any of the experimental manipulations often resulted in systolic vibrational complexes of an intensity too low to be heard.

<div align="center">COMMENT</div>

In evaluating the results of these experiments, it is necessary to re-emphasize the fact that in all of them the factor of tensing of the

auriculoventricular valves was eliminated. In the case of the iso-
metrically contracting heart, the muscle contracted against a fixed
volume of blood within the ventricles. In this instance the degree of
pressure brought to bear against the contracting muscle was dependent
upon the force of myocardial contraction and represented the maximum
force of which it was capable. When the venae cavae were clamped, the
intraventricular pressure was rendered nil and the myocardium con-
tracted against no force. These represent the extremes of the degree of
tension developed by the myocardium. Placing balloons within the ven-
tricles prevented the normal motion of the auriculoventricular valves
and permitted the ventricles to contract against a known, fixed pressure.
In each case, contraction of the heart muscle was accompanied by a
sound (as long as vigor of the contractions was maintained) and by
definite, low-frequency vibrations with a steep (audible) slope, as
recorded by the vibrocardiograph. Examination of the curves shows
that the vibrations, including the audible sound, occur just before, or at
the peak of, the R wave of the electrocardiogram. This would seem to
indicate that the vibration and sound occurred at a time when the state
of the muscle changed from diastolic relaxation to one of sudden tensing.

These experiments appear to indicate that myocardial contraction
produces a vibration complex which may be audible. Palfrey[3] thought
that the first sound occurs when the heart muscle and A-V valves sud-
denly tense en masse under the impact of contraction, and he compared
the ventricle to a piece of lax cloth suddenly brought under tension
during systole. Schutz[5] held a similar view. Wiggers[6] demonstrated
that small, isolated strips of ventricular muscle from the hearts of cats,
when made to contract, produced a sound. He regarded this sound as
the result of bringing the muscle fibers to a state of sudden tautness.
More recently, Eckstein[4] perfused isolated, V-shaped strips of cat ven-
tricular muscle through the left descending coronary arteries. Vibra-
tions, in part audible, were recorded from the muscle strip as it con-
tracted, and, on auscultation, sounds like feeble first heart sounds could
be detected. He found, however, that no sounds occurred during strictly
isometric contraction. In our "isometric" preparations there was
usually a slight, but definite, change in the size of the ventricle during
systole, no matter how tightly the A-V ligature was drawn; that is, the
heart was probably not contracting isometrically in the strictest sense.
This latter observation of Eckstein's, therefore, cannot be held as neces-
sarily contradictory to our own.

Since small segments of ventricular muscle produce vibrations during
contraction, it would appear quite possible that, in a large ventricular
mass, the tensing of the muscle fibers in concert might produce marked
vibrations and well-defined sounds. One might visualize the muscle fibers
as many lax cables, which, when suddenly stretched, are set into vibra-
tion. The degree of force applied to the fibers would, of course, in-
fluence the intensity of the vibrations. In our experiments, at any rate,

well-defined muscle vibrations were recorded while the vigor of myo-
cardial contraction was maintained, and diminished as the muscle failed.

Dock[2] reported that in the heart which had been deprived of blood
flow by clamping the venae cavae, or in the "isometrically" beating
heart, the vibrations concurrent with systole were diminished more than
90 per cent. He believed that the small vibrations which he recorded
under these conditions were merely inaudible mechanical effects of
muscle contraction. These observations are at variance with our own,
for our records were taken at about two times the audible threshold;
furthermore, after the beginning of the experimental procedure systolic
sounds were still audible. Hence, there was not a 90 per cent diminution
in sound intensity. Likewise, systolic sounds were easily audible by
ordinary means of auscultation, as anyone may note.

SUMMARY

Studies were made on the muscular elements in the first heart sound,
using hearts of dogs, by eliminating normal movement and tensing the
auriculoventricular valves. This was accomplished by occluding the
venae cavae, by tensing a ligature around the auriculoventricular sulcus
to produce an "isometrically" contracting heart, or by inflating small
balloons in the ventricular cavities to pressures of 50 mm. Hg or more.

It was found that muscular sounds could be recorded and heard as
long as the vigor of myocardial contraction was maintained. The pos-
sible mechanism underlying the phenomenon is discussed.

REFERENCES

1. Kountz, Wm. B., Gilson, A. S., and Smith, J. R.: The Use of the Cathode Ray
   for Recording Heart Sounds and Vibrations. I. Studies on the Normal
   Heart, AM. HEART J. 20: 667, 1940.
2. Dock, W.: Mode of Production of the First Heart Sound, Arch. Int. Med. 51:
   737, 1933.
3. Palfrey, F. W.: The Cause of the First Heart Sound, New England J. Med.
   200: 1917, 1929.
4. Eckstein, R. W.: Sounds Due to Muscular Contraction and Their Importance
   in Auscultatory Qualities of the First Heart Sound, Am. J. Physiol. 118:
   359, 1937.
5. Schutz, E.: Experimentelle Untersuchung über die Entstehung der Herztöne,
   Ztschr. f. d. ges. exper. Med. 77: 348, 1931.
6. Wiggers, C. J.: Modern Aspects of the Circulation in Health and Disease,
   ed. 2, Philadelphia, 1923, Lea & Febiger, p. 319.
   Wiggers, C. J.: Factors Determining the Relative Intensity of the Heart
   Sounds in Different Auscultation Areas, Arch. Int. Med. 24: 471, 1919.
7. Smith, J. R., Kountz, Wm. B., and Gilson, A. S.: A Consideration of Extra-
   Valvular Elements in the First Heart Sound, Proc. Soc. Exper. Biol. & Med.
   43: 256, 1940.

THE EFFECT OF INTRAVENOUS INJECTION OF PAPAVERINE HYDROCHLORIDE UPON THE MORTALITY RESULTING FROM SUDDEN OCCLUSION OF CORONARY ARTERIES IN DOGS

C. G. McEachern, M.D., F. H. Smith, M.D., and G. W. Manning, M.D.
Toronto, Can.

IN A previous paper,[1] the effects of sudden occlusion of coronary arteries on conscious and anesthetized dogs were described. It was shown that, in the conscious animal, ligation of the circumflex branch of the left coronary artery resulted in a mortality of 75 per cent, and that ligation of the smaller anterior descending branch resulted in a mortality of 40 per cent. In the same paper it was reported that anesthesia (ether and morphine) reduced the mortality from 75 per cent to 25 per cent in the case of the left circumflex, and from 40 per cent to less than 10 per cent in the case of the left anterior descending branch.

We have shown, also, that unilateral and bilateral sympathetic denervation of the heart reduces the mortality.[2] After unilateral denervation, the mortality caused by ligation of the left circumflex branch was reduced to 33 per cent. Bilateral denervation further decreased the mortality to 10 per cent.

When ligation of either the left circumflex branch or anterior descending branch of the left coronary artery proves fatal, characteristic sequences of electrocardiographic events are always observed. Ligation of the left circumflex branch is followed by a progressive rise of the R-T segment from the isoelectric level in Lead II (Fig. 1). Extrasystoles soon appear, and are followed, after varying periods of time, by ventricular tachycardia and fatal ventricular fibrillation. When the anterior descending branch is ligated, the S-T segment becomes progressively depressed in Lead II. This is followed by extrasystoles, ventricular tachycardia, and ventricular fibrillation, in that order (Fig. 2).

From our earlier experiments we had tentatively assumed that when occlusion of a large coronary branch occurred there was also a widespread reflex spasm of the rest of the coronary arterial system, particularly of the smaller arterioles which are innervated by the vagus. It was believed that this reflex mechanism was activated by metabolites produced in the ischemic area, which, by initiating afferent impulses, gave rise to reflex efferent vagal impulses, and thus caused vasoconstriction of the medium- and smaller-sized coronary arteries. On the other hand, it is possible that certain areas of the

myocardium are more sensitive to ischemia than others, and that ectopic beats, ventricular tachycardia, and ventricular fibrillation are more readily initiated when the blood supply to these areas is reduced.
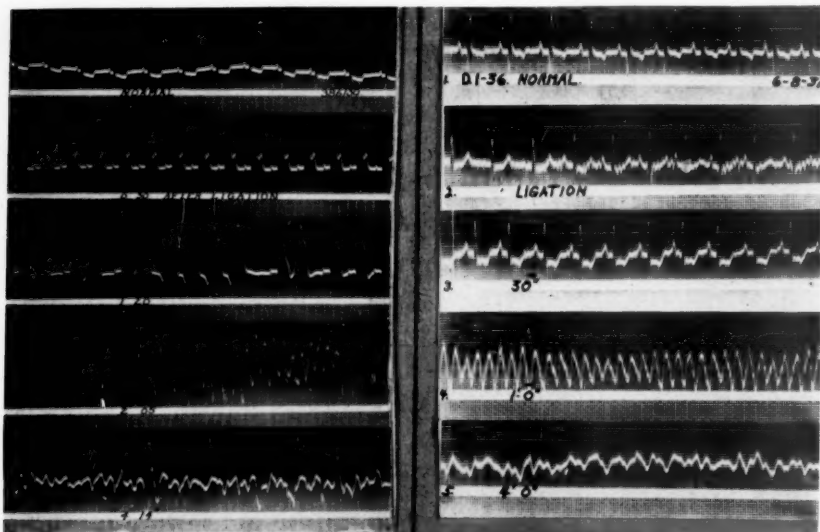

Fig. 1.   Fig. 2.

Fig. 1.—Lead II, showing changes following ligation of the circumflex branch of the left coronary artery of the conscious dog. Note the early elevation of the R-T segment. Fatal ventricular fibrillation.

Fig. 2.—Lead II, showing changes following ligation of the anterior descending branch of the left coronary artery of the conscious dog. Note the early depression of R-T segment. Fatal ventricular fibrillation.

The marked reduction in mortality achieved by anesthesia (ether and morphine), as well as by sympathetic denervation of the heart, apparently resulted from interference with the sequence of events which terminate in ventricular fibrillation. We therefore feel that the immediate treatment of angina pectoris and coronary occlusion should be directed toward (1) release of any possible spasm of coronary arteries, (2) subsequent dilatation of these vessels, and (3) depression of the fibrillation mechanisms.

In view of the fact that papaverine hydrochloride is reputed to relieve spasm in smooth muscle and also has a sedative effect, it would appear that it might help to prevent death following sudden occlusion of coronary arteries. Pal,[3] in his experimental investigation of papaverine, concluded that the drug relaxed smooth muscle by a direct action on the muscle fibers. He found that in arteries under normal tone the relaxing effect was negligible, but that if vasoconstriction were present this relaxing effect was quite marked. Adler[4] and Macht[5] have confirmed these observations. Macht[5] investigated the action of papaverine and found that it caused a marked dilatation of

the coronary, splanchnic, and peripheral vessels. He also found that it relaxed smooth muscle without producing paralysis. As an analgesic, papaverine is more effective than codeine but less effective than morphine.

In recent years there have been many reports that papaverine releases the vascular spasm which is believed to accompany arterial embolism or thrombosis. Denk[6] treated several patients with arterial embolism of the extremities with eupaverine (closely related to papaverine), with excellent results. Allen and MacLean[7] also used it successfully in one case. De Takats[8] has reported similar successes. More recently, De Takats, Beck, and Fenn[9] have advocated the use of papaverine to relieve the vascular spasm which they believe accompanies pulmonary embolism.

Because of the pharmacologic actions of papaverine, and the fact that, clinically, it is said to relieve vascular spasm, we wondered whether it might not decrease the mortality caused by occlusion of coronary arteries in conscious animals. Experiments to decide this question were undertaken. Since the mortality which resulted from ligation of the left circumflex branch was higher than that caused by ligation of the anterior descending branch, only the left circumflex was ligated in the experiments reported in this paper.

EXPERIMENTAL PROCEDURE

Normal, healthy dogs were used. Under intratracheal anesthesia, the thorax was opened through the fourth intercostal space and the heart exposed. A loose ligature was placed around the circumflex branch of the left coronary artery, and the ends allowed to protrude through the skin at each end of the incision in the thorax. The animals were then allowed to recover. The following day papaverine hydrochloride (11 mg./kg. body weight) was injected intravenously, and the ligation carried out on the conscious animal by traction on the ends of the loose ligature. Electrocardiograms were taken prior to operation, before and after administration of the drug, before ligation, and intermittently for some time afterward.

Twenty dogs were used in these experiments. Nine died within seventeen minutes of the ligation, and eleven survived. This gave a probable mortality of 45 per cent. One of the dogs which survived the initial ligation died about eight hours later. The remaining ten dogs survived indefinitely, so that the twenty-four-hour mortality was probably 50 per cent.

Frequently, after the intravenous injection of papaverine, the animal struggled violently for a few moments. This struggling was associated with respiratory distress, and transitory cyanosis was often observed. Following this reaction the animals lay quietly. Subsequent ligation produced evidence of cardiac pain. This pain, however, was less severe than that experienced by animals which had received no papaverine prior to ligation.

ELECTROCARDIOGRAPHIC CHANGES

Other than a slight bradycardia, no characteristic changes were observed in the electrocardiograms as a result of the intravenous injection of papaverine.

The electrocardiograms of the animals which died (Fig. 3) showed changes similar to those that were observed when no papaverine was administered prior to the ligation of the circumflex branch of the left coronary artery of the conscious animal (Fig. 1). In Lead II, the R-T segment showed, with varying rapidity, a progressive elevation above the isoelectric level. Extrasystoles, chiefly of right ventricular origin, appeared, and were followed by ventricular tachycardia and fatal ventricular fibrillation.
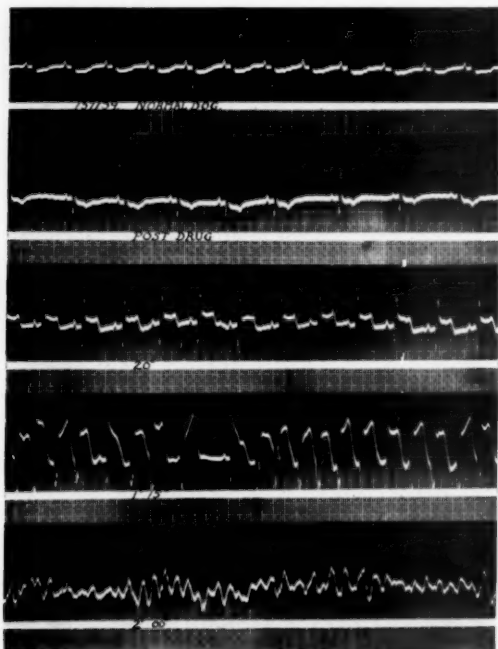

Fig. 3.—Lead II, showing changes following ligation of the circumflex branch of the left coronary artery of a dog previously injected with papaverine. Fatal ventricular fibrillation.

The electrocardiograms of the surviving animals showed, in several instances, many gross irregularities (Fig. 4). The R-T segment rose typically, and extrasystoles of both right and left ventricular origin were seen. Runs of ventricular tachycardia were observed frequently, and in four of the animals the ventricular tachycardia was fairly persistent.

COMMENTS

In these experiments papaverine hydrochloride was given in larger doses than have been advised for clinical use in cases of arterial embolism. However, this dose (11 mg./kg. body weight) was used so that a maximal effect could be observed.

It would appear that papaverine in the dose used reduced the twenty-four-hour mortality from 75 per cent to 50 per cent. This reduction in

mortality may have been effected by the sedative action, by the coronary
dilator action, by the vascular antispasmodic action, or by any combina-
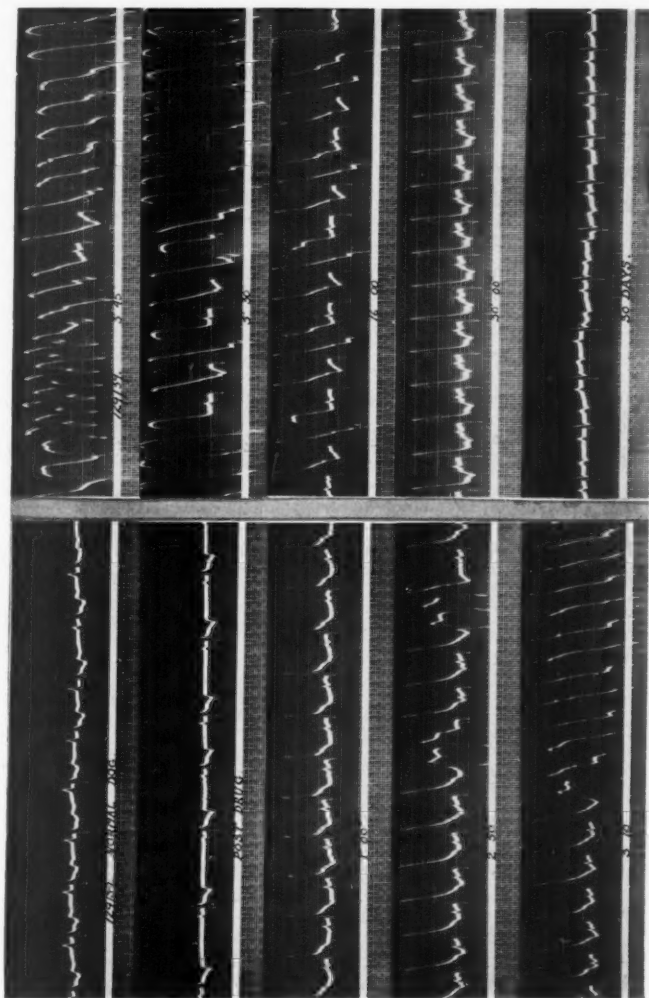tion of these actions of papaverine.

Fig. 4.—Lead II, showing changes following ligation of the circumflex branch of the left coronary artery of a dog previously injected with papaverine. Note the marked irregularities. Survival type of record.

Although the injection of papaverine does not produce any charac-
teristic change (other than slowing) in the electrocardiogram, there were
certain significant differences between the electrocardiograms of these
animals after ligation of the circumflex branch of the left coronary
artery and those of untreated animals which had been subjected to
similar coronary artery ligation.

In the records of the latter group, the characteristic sequence of
events, over a varying length of time, is progressive elevation of the R-T
segment, extrasystoles, ventricular tachycardia, and ventricular fibrilla-
tion. However, when extrasystoles become numerous ventricular tachy-

cardia practically always follows, and this is usually succeeded by ventricular fibrillation. In these untreated animals, recovery after a run of ventricular tachycardia is, in our experience, rare. However, of the animals which had received papaverine, four recovered after persistent ventricular tachycardia. Although all of the animals which survived showed marked cardiac irregularities, it was apparent that the stage of ventricular tachycardia was not reached in all cases, and that, in some of those in which it was, the animal was able to recover before ventricular fibrillation ensued.

It is recognized that papaverine has a sedative action, but, in these experiments, its effectiveness as an analgesic in reducing cardiac pain, although definite, was not great.

SUMMARY

1. Papaverine hydrochloride, as used in these animal experiments, reduced the twenty-four-hour mortality caused by coronary artery ligation from 75 per cent to 50 per cent.

2. Papaverine hydrochloride interrupts, to some extent, the sequence of electrocardiographic events which occur after ligation of the circumflex branch of the left coronary artery.

3. Papaverine hydrochloride, even in large doses, does not completely abolish cardiac pain.

4. Papaverine hydrochloride, when injected intravenously in large doses, frequently causes respiratory distress, with cyanosis, which is not fatal.

REFERENCES

1. Manning, G. W., McEachern, C. G., and Hall, G. E.: Reflex Coronary Artery Spasm Following Sudden Occlusion of Other Coronary Branches, Arch. Int. Med. **64:** 661, 1939.
2. McEachern, C. G., Manning, G. W., and Hall, G. E.: Effects of Sudden Occlusion of Coronary Arteries Following Removal of the Cardio-Sensory Pathways, Arch. Int. Med. **65:** 661, 1940.
3. (a) Pal, J.: Papaverin und Eupaverin, Deutsche med. Wchnschr. **56:** 1702, 1930.
   (b) Pal, J.: Experimentelle und klinische Studien über die Wirkung des Papaverins, Wien. med. Wchnschr. **63:** 1050, 1913.
4. Adler, L.: Untersuchungen zur Pharmakologie der Gefässe, Arch. f. exper. Path. u. Pharmakol. **91:** 81, 1921.
5. Macht, D. I.: A Pharmacologic and Clinical Study of Papaverine, Arch. Int. Med. **17:** 786, 1916.
6. (a) Denk, W.: Zur Behandlung der arteriellen Embolie, München med. Wchnschr. **81:** 437, 1938.
   (b) Denk, W.: Weitere Erfahrungen mit der unblutigen Behandlung der Embolie, Zentralbl. f. Chir. **63:** 2, 1936.
7. Allen, E. V., and MacLean, A. R.: Treatment of Sudden Arterial Occlusion With Papaverine Hydrochloride, Proc. Staff Meet. Mayo Clinic **10:** 216, 1935.
8. De Takats, G.: The Use of Papaverine in Acute Arterial Occlusion, J. A. M. A. **106:** 1003, 1936.
9. De Takats, G., Beck, W. C., and Fenn, G. K.: Pulmonary Embolism, Surgery **6:** 339, 1939.

THE TETRALOGY OF EISENMENGER*

OTTO SAPHIR, M.D., AND MAURICE LEV, M.D.
CHICAGO, ILL.

THE number of congenital cardiac anomalies which permit survival until adulthood is relatively limited (Abbott[1]). Among these may be mentioned cor biatriatum triloculare, with or without transposition, and with or without tricuspid atresia; bicuspid aortic valve; coarctation of the aorta; right or double aortic arch; patent ductus arteriosus; defects of the auricular and ventricular septa, with or without congenital mitral stenosis (Lutembacker's disease); pulmonary stenosis without transposition; the tetralogy of Fallot; and the tetralogy of Eisenmenger. As has been pointed out by Abbott, many of these conditions are at the present time diagnosable by means of clinical and roentgenologic signs, and by exclusion.

We recently had the opportunity to perform a post-mortem examination on a young adult with an Eisenmenger complex. In view of the relative rarity of this condition, and because of the possibility of recognizing this type of congenital heart disease clinically, we thought that it might be of interest to report this case. Besides, this anomaly has certain aspects which may help to clarify our understanding of transposition in general. Primarily for this reason, the anatomic features of the heart are stressed, and a detailed embryologic explanation is presented.

The tetralogy of Eisenmenger, or the Eisenmeyer complex, or the tetralogy of Fallot (Eisenmenger variety) consists of (1) dextraposition of the aorta, (2) defect of the interventricular septum, (3) right ventricular hypertrophy, and (4) dilatation of the pulmonary artery. It thus differs from the tetralogy of Fallot in that there is dilatation of the pulmonary artery instead of stenosis of the pulmonary orifice.

Although the tetralogy of Fallot is not infrequently seen in hearts of adults, the tetralogy of Eisenmenger is relatively rare. Cases have been reported by Eisenmenger[2] (1897), Abbott[3] (1925), Abbott[4] (1927), Baumgartner and Abbott[5] (1929), Stewart and Crawford[6] (1933), Rosedale[7] (1935), Talley and Fowler[8] (1936), and Millman and Kornblum[9] (1936). The pertinent details of these reports are presented in Table I.

REPORT OF CASE

A 21-year-old white man was admitted to Michael Reese Hospital Nov. 3, 1939, and died the same day. He was born a blue baby, and had been an invalid all of his life because of dyspnea on moderate exertion. His early development was retarded; at the age of 2 he was unable to walk or talk. He managed to reach the eighth grade of grammar school. He was subject to frequent sore throats, and, at the age

TABLE I

Cases of Eisenmenger Complex Previously Reported

AUTHOR	DATE	AGE	SEX	PERTINENT CLINICAL DATA	POSITION OF AORTA	OTHER IMPORTANT PATHOLOGIC CHANGES	CAUSE OF DEATH
Eisenmenger	1897	32	M	Cyanosis during youth, with some dyspnea on exertion. Slight clubbing of fingers. Systolic murmur over middle of heart, not heard above its base nor along the course of the aorta, but transmitted to the right and inferiorly and to the apex. Diastolic murmur at lower end of sternum in terminal stage.	Riding aorta	Ductus arteriosus closed. No coarctation. Foramen ovale closed.	Heart failure
Abbott (Libman)	1925	33	M	Heart trouble at age of 5. Dyspnea and pain in chest on admission to hospital. Loud, rough, systolic murmur heard over entire precordium, with maximum intensity within left nipple line. P_2 not accentuated. Systolic thrill at apex. Some clubbing of fingers.	Riding aorta	Slight coarctation of the aorta. Possibly congenital aneurysm of the membranous septum. Old endocarditis of the aortic valve, with insufficiency. Old endocarditis of the mitral valve. Subacute bacterial endocarditis involving aortic and mitral valves and defect of interventricular septum present in the aneurysm. Foramen ovale closed.	Subacute bacterial endocarditis
Abbott	1927			Eight cases of dextroposition of the aorta without stenosis of the pulmonary artery. Of these patients, four had dilatation of the pulmonary artery and two showed hypoplasia of the aorta. Mention is made of an infant, aged 15 months, with the typical Eisenmenger complex.			
Baumgartner and Abbott	1929	20	M	Lack of endurance, dyspnea on exertion, cyanosis for some time. Hoarseness and aphonia. For 7 years, loud, harsh, systolic murmur over pulmonic area. Diastolic murmur to left of sternum.	Riding aorta	Pulmonary cusps of unequal size, with fenestration. Small accessory coronary artery, arising from pulmonary artery. Slight conus stenosis. Thick muscle bundles of conus. Paradoxical embolus, with brain abscess.	Paradoxical embolus

Stewart and Crawford	1933	60	M	No dyspnea or cyanosis during life. No clubbing of fingers. Marked terminal cyanosis, with dyspnea. Soft, blowing, systolic murmur at apex. Hypertension. Marked right and left ventricular failure.	Riding aorta	Healed pulmonary valvulitis and arteritis.	Heart failure
Rosedale	1935	10	M	Transient cyanosis at birth. Cyanosis and dyspnea on exercise thereafter. Moderate clubbing of fingers. Systolic murmur at apex.	Riding aorta	Patent foramen ovale. Ductus arteriosus closed. Hypoplasia of the aorta.	Heart failure
Talley and Fowler	1936	31	F	Blue baby. Dyspnea on exertion throughout life. Cyanosis became worse after two pregnancies. Marked clubbing of fingers. Hoarseness for many years. Systolic, and, at times, diastolic thrill at midsternum. Diastolic thrill sometimes at third left intercostal space. Low-pitched diastolic murmur constantly heard at pulmonary region, which could be traced down to apex. Systolic murmur also heard at apex and midsternum, but not transmitted to base.	Riding aorta	Hypoplasia of the aorta. Hypertrophy of crista. Pulmonary cusps thickened and rounded.	Heart failure
Millman and Kornblum	1936	32	F	Slight cyanosis, slight clubbing of fingers. Double thrill—systolic and diastolic—at pulmonic area. Loud, rough, systolic murmur, with slight diastolic phase, at pulmonic, transmitted slightly to clavicle. P_2 not heard.	Riding aorta	Subacute bacterial endocarditis of the pulmonic valve. Foramen ovale closed.	Subacute bacterial endocarditis

of 10, had joint pains with no accompanying fever. He had never received medical care until two weeks before admission, when his dyspnea became more marked. A physician prescribed digitalis, but the patient became worse and was sent to the hospital. On admission his pulse was imperceptible; the temperature was 101°, and the respiratory rate was 40 per minute. His blood pressure could not be measured. He was poorly developed and undernourished, orthopneic, dyspneic, cyanotic, restless, perspiring, and too weak to answer questions. There was marked clubbing of the fingers and toes. The throat was injected, with prominent vessels about the large, cryptic tonsils. Three petechiae were seen on the soft palate. A few râles were present at the base of the right lung. There was bulging of the lower end of the sternum. The heart was enlarged; its transverse diameter extended from the left axillary to the right midclavicular line. There was marked prominence of the pulmonary conus, in which region a diastolic thrill was felt and a loud blowing systolic murmur was heard. A blowing murmur was also heard at the apex; it was difficult to time because of the rapid rate (166). Heart tones were audible along the entire spine. The liver was enlarged, extending to the umbilical region, and was firm and very tender. The spleen was not palpable.

The patient died suddenly, five hours after admission. The clinical diagnoses were: congenital heart disease (tetralogy of Fallot); rheumatic stenosis of the mitral orifice, with insufficiency of the valve and enlargement of the left auricle; congestive heart failure, with auricular fibrillation. Subacute bacterial endocarditis was also considered.

POST-MORTEM EXAMINATION

Heart (Figs. 1, 2, and 3).—The heart was markedly enlarged to the right and left; its transverse diameter was two-thirds that of the chest cavity, and it weighed 450 Gm. The apex was formed by the right ventricle. From the base two vessels were seen to emerge, a smaller to the right and slightly anterior, and a larger to the left and somewhat posterior. Many single and confluent, opaque, grayish-white patches were present on the pericardial surface of the base of these two vessels. Two auricular appendages were noted adjacent to each other on the right anterior aspect of the heart, one lying superior and to the left of the other. The mutual relationships of the various heart chambers were normal.

The right auricle was moderately dilated and its wall distinctly thickened, measuring as much as 0.3 cm. in thickness. The superior and inferior venae cavae and the coronary sinus entered this chamber normally. The eustachian and thebesian valves were normal. The limbus, instead of the usual arc, with a large horizontal diameter, presented an arc with an enlarged vertical diameter. The foramen ovale was closed, and there was no defect of the auricular septum. It was now noted that the auricular appendage which lay inferior and to the right was the right auricular appendage. The endocardium of the right auricle presented no remarkable changes.

The tricuspid orifice measured 14.5 cm. in circumference. The leaflets of the tricuspid valve, although normally formed, were somewhat thickened. The corresponding chordae tendineae were likewise somewhat thickened, but presented no further change. There was no posterior papillary muscle; the anterolateral papillary muscle was normal.

The right ventricular chamber was distinctly larger than normal. Its wall measured 1.2 cm. in thickness. From the base of the ventricle the two vessels noted externally emerged, each with its own ventricular outflow portion. The artery to the right and slightly anterior was the aorta, and the one to the left and slightly posterior was the pulmonary artery. The aortic orifice measured 8 cm. in circumference. The aortic valve consisted of three well-formed cusps, one situated to the

left, one anterior and to the right, and one posterior and to the right. The non-coronary cusp was the right anterior. The aortic cusps were markedly fenestrated throughout, and thickened at their line of closure. The aorta gave off the brachio-cephalic vessels normally. In the region of the distal part of the isthmus, the lumen
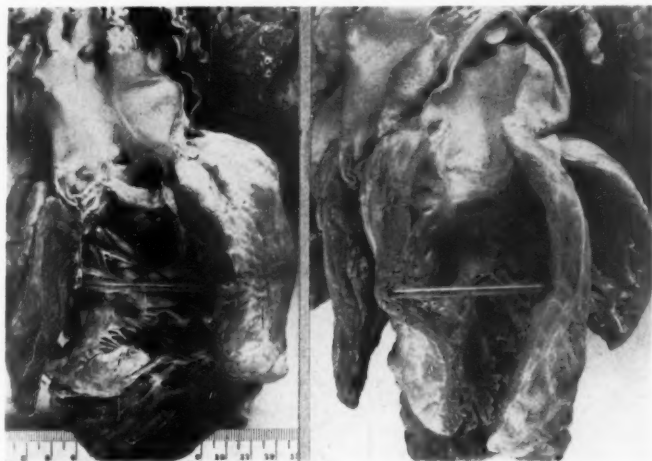

Fig. 1. Fig. 2.

Fig. 1.—Right ventricular view of the heart, exposing the mouth of the aorta. Note the aorta coming off the right ventricle, the septal defect just below the aortic valve, and the leaflets of the tricuspid valve.

Fig. 2.—Right ventricular view of the heart, exposing the infundibulum. Note the muscular arch separating the infundibulum from the outlet of the right ventricle lead-ing into the aorta (above the glass rod).

Fig. 3.—Left ventricular view of the heart. Note the interventricular septal defect and the stenosis of the mitral orifice (not opened).

of the aorta was distinctly constricted, measuring only 5 cm. in circumference. The ductus arteriosus was widely patent. The bronchial arteries were not enlarged. The circumference of the descending aorta was distinctly diminished. The orifice of the

pulmonary artery measured 9.6 cm. in circumference. It was thus distinctly larger than the aorta. Its valve consisted of three cusps—one right, one anterior and to the left, and one posterior and to the left. The cusps showed no remarkable changes. The lumen of the pulmonary artery was larger than that of the aorta. The two pulmonary arteries arose normally.

The topography of the muscle bundles of the right ventricle was distinctly abnormal. The moderator band was thick, and merged with the septal muscle bundle, which was likewise markedly thickened. This bundle ascended obliquely upon the septum toward the base of the ventricle, where it formed an arch of muscle over the roof of the ventricle; this arch then descended obliquely and laterally over the anterior wall of the right ventricle. Thus the septal muscle bundle formed a complete arch which separated the two outflow portions of the right ventricle. The parietal muscle bundle, however, was not present. The pars membranacea septi ventriculorum was absent. The adjacent musculature of this septum was likewise defective, producing an opening in the interventricular septum which measured 2 cm. in its greatest diameter. The defect faced the aorta, and was separated from the outflow portion of the pulmonary artery by the arched musculature of the septal muscle bundle.

The left auricular chamber was not as large as the right; its wall measured 2 mm. in thickness. It received the four pulmonary veins normally. The left auricular appendage was not present in its normal position to the left of the normally placed aorta, but emerged from a more posterior position to the right of the dextraposed aorta. This was the abnormal appendage which was seen superiorly and to the left of the right auricular appendage on the anterior wall of the right auricle.

The mitral valve leaflets and their corresponding chordae tendineae and papillary muscles were normally formed. However, the leaflets were markedly thickened at their line of closure, and were mutually adherent, as were their chordae, thus producing a funnel-shaped opening of the mitral orifice which measured only 4.5 cm. in circumference.

The left ventricular chamber was about normal in size. Its wall measured 1.1 cm. in thickness. Numerous, atypical chordae bridged the cavity of this chamber; they originated from the papillary muscles and were inserted on the septum. The only outlet from this chamber was the defect in the interventricular septum. The rim of this defect presented a thickened endocardium on its left ventricular aspect which formed a ledge, especially in its inferior portion.

The left coronary artery arose from the right posterior sinus of Valsalva. The right coronary artery was represented by two separate vessels, each with a separate ostium; both ostia arose from the left sinus of Valsalva. The left coronary artery gave rise to a branch which passed obliquely downward over the right ventricle toward the apex, and terminated some distance above the apex. The remainder of the left coronary artery formed a small branch which ran in an oblique direction to the superior wall of the right ventricle. The larger, right coronary artery curved around the posterior wall of the pulmonary artery, gave off branches to the septum, and then divided into an anterior descending branch and a large ramus marginis obtusi. The smaller, right coronary artery ran in the anterior atrioventricular sulcus to the acute margin of the heart; it gave off the ramus anterior ventriculi dextri, and terminated as the ramus acutus. There was no posterior descending branch.

The diagnoses, as far as the heart was concerned, were: (1) partial transposition of the great arterial trunks (Rokitansky), transposition type II (Spitzer), tetralogy of Eisenmenger; (a) origin of the aorta and pulmonary artery from the right ventricle; (b) defect of the interventricular septum; (c) dilatation of the pulmonary artery; (d) coarctation of the aorta; (e) patency of the ductus arteriosus; (f) abnormally formed left auricular appendage; (g) atypical coronary artery distribution; (h) abnormal topography of the musculature of the right ventricle;

(2) old endocarditis of the mitral valve, with insufficiency of the valve and stenosis of its orifice; and (3) hypertrophy of the heart—right auricle and ventricle, marked, and left auricle, moderate.

In addition, there were (1) moderate kyphoscoliosis, (2) moderate emphysema, (3) chronic passive hyperemia of the lungs, liver, spleen, kidneys, and gastrointestinal tract, and (4) clubbing of the fingers and toes.

COMMENTS

The knowledge that certain anomalies occur together leads us to attempt to discover symptoms, physical signs, and other data which may enable us to make a correct clinical diagnosis and an accurate prognosis, and to institute intelligent treatment. Pathologically, the knowledge that a complex exists is the starting point for an investigation of the embryologic variant in the development of the heart which was responsible for the anomaly.

Thus, the realization by Farre,[10] Peacock,[11] and Fallot[12] that dextraposition of the aorta, a defect of the ventricular septum, pulmonary stenosis, and right ventricular hypertrophy represent a pathologic complex, and constitute the most frequent anomaly found in adults, eventually made the clinical diagnosis possible. Likewise, the realization that there may be dilatation of the pulmonary artery instead of the more usual stenosis has led to the possibility of differentiating clinically between the tetralogy of Eisenmenger and that of Fallot. Clinically, the most important differences between the two conditions are as follows: (1) there are relatively less cyanosis and clubbing of the fingers in cases of the Eisenmenger complex; (2) hoarseness may occur in cases of the Eisenmenger complex, but not with the tetralogy of Fallot (Baumgartner and Abbott,[5] Talley and Fowler[8]); (3) pulmonic insufficiency, with a diastolic murmur, occurs in some cases of the Eisenmenger complex, but not with Fallot's tetralogy (Baumgartner and Abbott,[5] Talley and Fowler,[8] Millman and Kornblum[9]); (4) accentuation of the pulmonary conus, as shown roentgenologically and by percussion, is much more marked with the Eisenmenger complex than with the tetralogy of Fallot, and the silhouette resembles that caused by uncomplicated auricular and large ventricular septal defects, and, to a lesser extent, by an auricular septal defect with mitral stenosis (Lutembacker's disease); (5) there is possibly a difference in the transmission of the systolic murmur in the two conditions. In the case reported by Eisenmenger, the murmur was heard over the middle of the sternum, and was transmitted to the right, inferiorly, and to the apex, but not to the neck. The transmission was similar in the case of Talley and Fowler. In the cases of Millman and Kornblum, and Baumgartner and Abbott, the systolic murmur was heard at the pulmonic area, and, in the former, was transmitted slightly to the clavicle (left?). In the case reported by Abbott, the systolic murmur was heard over the entire precordium, and was of maximum intensity over the left nipple. In the cases of Stewart and Crawford, and Rosedale, a systolic murmur was heard over the apex. No mention is

made of lack of transmission of the murmur to the neck in any of the cases except that of Eisenmenger. V. Schroetter[13] (who detected the absence of pulmonary stenosis in the case of Eisenmenger) considered that, when there is a ventricular septal defect with stenosis, the murmur may be transmitted to the neck because of flow of blood from the right to the left ventricle, whereas, if the defect were unaccompanied by stenosis, the flow of blood would be from left to right (except in the terminal phase), and therefore the murmur would not be transmitted to the neck. It is possible that this may be a differentiating point between the tetralogies of Fallot and Eisenmenger. There are, however, at the present time insufficient data to draw definite conclusions on this point.

There are relatively less dyspnea and cyanosis with the Eisenmenger complex because, as Baumgartner and Abbott stated, the anatomic conditions are more favorable for oxygenation than is the case with the Fallot anomaly. In Eisenmenger's anomaly the aerated blood is carried from the left ventricle into the aorta directly (in riding aorta), or through the defect in the ventricular septum (as in our case). Because the arch of musculature at the base of the right ventricle demarcates the outflow tracts of the aorta and pulmonary artery, relatively little of this aerated blood gets into the pulmonary artery. The amount of unaerated blood which reaches the aorta varies with the position of the aorta. The unrestricted flow of blood through the pulmonary artery presents a marked contrast to Fallot's tetralogy, in which oxygenation in the lungs is insufficient because of the stenosis of the pulmonary orifice.

The hoarseness which occurs in some cases is caused by encroachment of the markedly dilated pulmonary artery on the recurrent laryngeal nerve, as pointed out by Talley and Fowler.[8]

It must be remembered that Eisenmenger regarded his case as one of uncomplicated patency of the interventricular septum. From his description of the relation of the pulmonary artery and aorta to the patency of the ventricular septum, it is quite clear that he was dealing with a riding aorta (Rokitansky), or type I transposition (Spitzer). Eisenmenger, however, overlooked this fact, which was later brought out by Abbott. Thus it is to Abbott that we owe the conception of what we now call the tetralogy of Eisenmenger, and not to Eisenmenger himself.

PATHOGENESIS OF THE EISENMENGER COMPLEX

From the pathologic standpoint, our understanding of this combination of anomalies has gone hand in hand with our conception of transposition. Since the time of Rokitansky[14] it has been generally agreed that in transposition complexes the primary anomaly is the transposition of the arteries, and, therefore, in the Eisenmenger complex the defect

in the ventricular septum and the dilatation of the pulmonary artery should be considered secondary. According to the theory of Rokitansky, the underlying embryologic variant in this complex is an abnormality in the rotation of the septum bulbi.

According to the theory of Spitzer,[15] this complex represents a sub-type of transposition type I or type II. Because of lack of sufficient torsion of the bulboventricular loop, migration and fusion of both primary bulbar septa are incomplete, with the result that the right ventricular aorta reopens. This, in turn, works to the disadvantage of the left aorta, which becomes obliterated. Thus, in the Eisenmenger complex, according to Spitzer, the aorta would have to be either a re-opened right ventricular aorta, or an as yet incompletely obliterated left aorta; if it were the latter, it would mean that the right aorta had not yet reopened.

In 1937, we reported six cases of transposition of the large arteries, with a complete summary of old and recent theories of transposition.[16] We pointed out our objections to the theories of Rokitansky,[14] Spitzer,[15] Keith,[17] and Pernkopf and Wirtinger.[18] We agreed, however, with the underlying hypothesis of Keith, namely, that transposition of the large arteries is caused by an abnormality in the absorption of the bulbus. Using the studies of Pernkopf and Wirtinger[18] on the movement of the heart during development as a basis, we formulated our own theory of transposition.

Pernkopf and Wirtinger[18] showed that the movements of the heart during development normally may be divided into two phases. The first phase is concerned with the formation of the auriculoventriculo-bulbar loop and the bulbar bayonet. At the end of this phase the bulbar ridges assume a spiral course of 270°. The large arteries, how-ever, are not as yet twisted about each other. The second phase is con-cerned with the absorption of the bulbus. This is brought about by two processes. Torsion of 150° (counterclockwise, looking truncusward from the bulbus) occurs at the distal bulbar ostium, which is accom-panied by back torsion of 45° (clockwise, looking bulbusward from the ventricle) at the proximal bulbar ostium. The twist of the bulbar ridges is thus reduced, and given to the truncus septum. The bulbus is short-ened and absorbed into the ventricles, and the arterial trunks now take on their definitive twist of 150° about each other.

We postulated that transposition is produced by an abnormality in the execution of the second phase, which, in turn, is caused by an ab-normality in the bulboauricular spur area. This permits an increased back torsion at the proximal ostium, which thus diminishes the necessity for torsion at the distal ostium. This results, grossly, in transposition.

Recently, after a study of truncus arteriosus communis persistens,[19] we re-evaluated our theory of transposition. We concluded that our fundamental hypothesis that we were dealing with an abnormality in the absorption of the bulbus was correct. However, we felt we had erred

as to the primary cause for this abnormal absorption. This is, most likely, not an abnormality in the bulboauricular spur, which we now regard as secondary, but an abnormality in the formation of ridge 3B.

Ridge 3B is phylogenetically the most recent formation in the bulbus, and is present only in birds and mammals. In the bulbus of the reptile, in addition to ridge 1A (which is present from the lungfish up), two opposite ridges are formed, namely, ridges 4B and 3C. In the transition from the reptile to the mammal, ridge 3B was apparently formed by the fusion of ridges 4B and 3C. Thus, whereas in the reptile the bulbus is divided into three parts, in the mammal it is divided into only two parts. The same is true of the truncus. Whereas in the reptile a septum aorticum and septum aorticopulmonale are formed, in the mammal only a single septum aorticopulmonale develops.
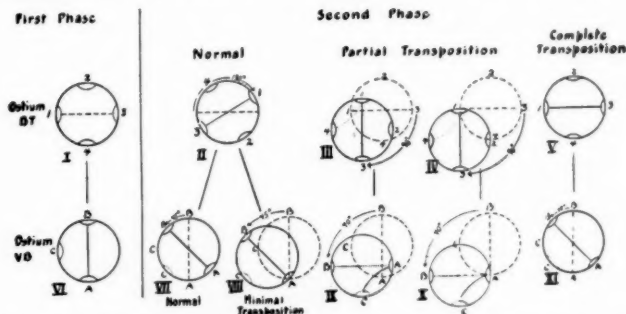

Fig. 4.—Absorption of the bulbus in transposition. There is an abnormality in the formation of ridge 3B, whereby it is poorly formed or replaced by ridge 4B or 3C. This results in decreased torsion at the distal ostium. In addition, this torsion occurs either around cushion 1, or close to cushion 1. At the proximal ostium, back torsion occurs around cushion A or close to cushion A. This back torsion may be 45°, or may reach 90°; the latter is normal in an earlier stage.

1, 2, 3, 4, Distal bulbar cushions; A, B, C, proximal bulbar cushions; BT, bulbotruncare (ostium); VB, ventriculobulbare (ostium); I, VI, distal and proximal bulbar ostia, respectively, at the end of the first phase (normal, and in transposition); II, VII, distal and proximal bulbar ostia during the second phase of normal absorption of the bulbus; II, VIII, bulbar ostia in transposition, with congenital aneurysm of the membranous septum during the absorption of the bulbus; III, IX, bulbar ostia in partial transposition during the absorption of the bulbus, when torsions center close to cushions 1 and A; IV, X, bulbar ostia in partial transposition during the absorption of the bulbus, when torsions center about cushions 1 and A; V, XI, bulbar ostia in complete transposition when no torsion occurs at the distal ostium, while mild back torsion occurs at the proximal ostium.

These differences within the embryonic truncus and bulbus result in gross differences in the definitive forms. Thus, in the reptile, the bulbus is absorbed almost completely, producing right and left ventricular aortae and a pulmonary artery with a defect of the ventricular septum; only a rim of bulbus musculature persists (Greil[20]). In the mammal, however, it is completely absorbed, which joins the pulmonary artery to the right ventricle and the aorta to the left ventricle, and closes the interventricular septum.

Transposition of the large vessels may be defined as that anomaly which occurs when the embryo of the mammal fails to carry out its most recent phylogenetic development, namely, the formation of ridge 3B

(Fig. 4). Instead, it retains either ridge 4B or 3C, forms an incomplete ridge 3B, or possesses only a solitary ridge 1A. The absorption of such a bulbus then proceeds abnormally. Because of either the absence of an opposite ridge, or lessened twist of the opposite ridge (either 4B or 3C), less torsion occurs at the distal ostium, and the torsion is excentric; the center of torsion is at a point between the center and cushion 1, or at cushion 1. The back torsion at the proximal ostium also occurs excentrically about a point between the center of the bulbus and cushion A, or about cushion A. This throws the aorta to the right, producing a riding aorta, or both the aorta and pulmonary artery emerge from the right ventricle, which constitutes partial transposition. In complete transposition, we postulate that, in addition to the absence of ridge 3B, ridge 1A either primarily fails to form, or secondarily becomes obliterated by the blood current. The absorption of such a bulbus, without ridges except at the proximal and distal bulbar ostia, consists purely of a process of telescoping and shrinkage, without torsions. This joins the aorta and pulmonary artery to the wrong ventricles.

ANALYSIS OF OUR CASE

The anatomic characteristics of our case were as follows: (1) both the aorta and pulmonary artery emerged from the right ventricle; (2) the diameter of the aorta was less than that of the pulmonary artery; (3) no artery emerged from the left ventricle, and, therefore, its only outlet was a defect in the interventricular septum; (4) coarctation of the aorta was present; (5) the ductus arteriosus was widely patent; (6) the left auricular appendage was abnormally formed and situated; (7) the coronary arterial ostia were displaced about 105° counterclockwise; (8) the coronary arterial distribution was abnormal; and (9) the muscle bundles of the right ventricle showed an abnormal configuration.

The fact that both the aorta and pulmonary artery arose from the right ventricle signified that we were dealing with a partial transposition (transposition type II, of Spitzer, or our Type C). The position of the coronary ostia showed that, during the second phase of the development of this heart (i.e., during the absorption of the bulbus), only 45° of torsion had occurred at the distal ostium, instead of the normal 150°. Also, according to our interpretation, this incomplete torsion at the distal ostium took place excentrically around cushion 1, or close to cushion 1 (Fig. 5). At the proximal ostium, back torsion also occurred excentrically around, or close to, cushion A. This caused both the aorta and pulmonary artery to arise from the right ventricle.

The reason for this abnormal absorption of the bulbus was that the mammalian ridge 3B failed to develop. Instead, the reptilian ridge 4B was formed. This produced, on the one hand, the abnormality in the absorption of the bulbus, and, on the other hand, the inequality in the size of the two arterial vessels (small aorta and large pulmonary

artery, Fig. 5). In the tetralogy of Fallot we believe that the reptilian ridge 3C is formed, thus producing a small pulmonary artery and a large aorta.

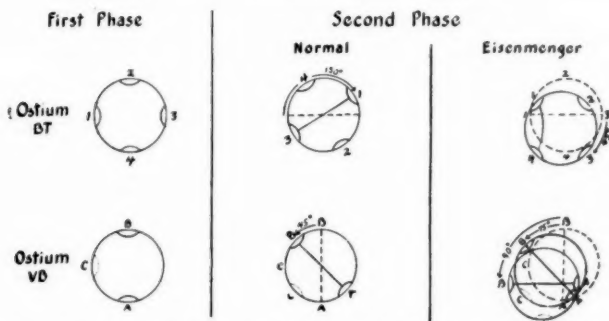### Absorption of the Bulbus in the Normal and in the Eisenmenger Complex

Fig. 5.—Absorption of the bulbus in the normal heart and in the Eisenmenger complex. Because of the formation of ridge 4B instead of 3B, a definitive bulbar septum, which consists of 4-1 at the distal ostium and A-B at the proximal ostium, develops. Because of the abnormal ridge 4B, the absorption of the bulbus proceeds abnormally. Normally, during this process there are a torsion of 150° (in the direction of the arrow) at the distal ostium, and a back torsion of 45° (in the direction of the arrow) at the proximal ostium. These torsions center around the bulbus. In the Eisenmenger complex, less torsion occurs at the distal ostium (BT), and this centers around cushion 1. Back torsion of 45° to 90° centers at the proximal ostium, around cushion A.
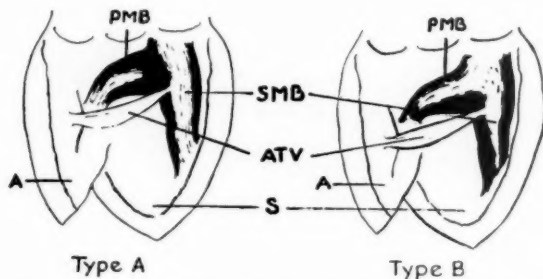

Type A   Type B

Fig. 6.—Normal topography of the muscle bundles of the right ventricle. *Type A*, Two distinct muscle bundles are noted. *Type B*, An arch of musculature is present at the base of the pulmonic valve.

SMB, Septal muscle bundle; *PMB*, parietal muscle bundle; *ATV*, anterior tricuspid leaflet; *A*, Anterior wall of the right ventricle; *S*, septal wall of the right ventricle.

A possible means of verifying this theory may be found by studying the topography of the muscle bundles. In our original work on transposition, because of confusing nomenclatures and conflicting conceptions of the muscle bundles of the right ventricle, we studied these muscle bundles in thirty-seven hearts from newborn infants. Two types of topography were noted (Fig. 6). In twenty-one cases there were two distinct muscle bundles, as pointed out by Keith.[24] From the septal cusp of the pulmonic valve, a muscle bundle descended obliquely over the septum toward the apex. This we called the septal muscle bundle. Near the apex it gave off the moderator band. On the anterior wall of

the right ventricle, the parietal muscle bundle ascended toward the base of the heart in close proximity to the anterior leaflet of the tricuspid valve. The superior portion of the muscle terminated at the septal cusp of the pulmonic valve. Its main intermediary portion fused with the musculature of the septum beneath the septal muscle bundle. There was a distinct raphe where the parietal muscle bundle dipped behind the septal muscle. The inferior portion terminated at the base of the anterior leaflet of the tricuspid valve. In the remaining sixteen cases there was a mass of musculature which formed an arch over the base of the ventricle at the base of the septal cusp of the pulmonic valve, with fibers radiating over the anterior wall of the right ventricle, adjacent to the

Fig. 7.—Muscle bundles of the right ventricle in the tetralogy of Fallot. The septal muscle bundle is hypertrophied. The parietal muscle bundle is minute or absent.

tricuspid, and down over the wall of the septum. In the human heart, therefore, it appears that we are dealing with two separate formations, namely, a parietal and a septal muscle bundle, and that these may become secondarily fused. Judging from the studies of Keith,[24] and Pernkopf and Wirtinger,[18] the formation of the parietal muscle bundle is related to that of the proximal bulbar septum, and is correlated with the presence and downward growth of ridge 3B. It is derived from cushion B, the bulboauricular spur, and the counter-ridge BO of the interventricular septum. The septal muscle bundle, according to Spitzer,[15] Fuchs,[21] Benninghoff,[22] Tandler,[23] and Keith[24] (with Pernkopf and Wirtinger[18] dissenting), is derived from ridge A, or C in A (see Spitzer).

The character of the muscle bundles of the right ventricle in congenitally abnormal hearts therefore affords us information concerning what took place during embryonic life. Spitzer[15] first pointed this out, and Humphreys[25] and we[16] have confirmed it. In the tetralogy of Fallot and truncus communis persistens, the septal muscle bundle is hypertrophied, while the parietal muscle bundle is small or almost absent (Fig. 7). In the tetralogy of Eisenmenger, however, there is often an arch of musculature over the base of the right ventricle which separates the outflow regions of the aorta and pulmonary artery (Fig. 2). In general, it has the topography of the normal, fused, septal and parietal muscle bundles, except that the parietal muscle bundle has no relationship to the anterior tricuspid leaflet, as is normally the case. This was noted by us in Case 2 of our series of transpositions, and occurred in the case reported herein; it was also present in the heart described by Talley and Fowler.[8] No adequate description of the muscle bundles is given by the other authors. Our previous interpretation was that this muscle bundle was purely a hypertrophied septal muscle bundle. It is now apparent to us that this arch of musculature incorporates an element of ridge 4B; therefore, it is the bulbar septum which has remained, demarcating that portion belonging to the aorta from that portion belonging to the pulmonary artery. If this is so, we are now able to locate point B, and to demonstrate that torsion at the proximal ostium occurred more or less around cushion A, which accounts for the fact that the aorta arose from the right ventricle. In the tetralogy of Fallot, however, the parietal muscle bundle is small or absent, because the opposite ridge in this case is 3C, not 4B. In transposition there may also be increased back torsion, amounting to 90°, at the proximal ostium about cushion A. Normally, such back torsion originally occurs during the second phase, but is secondarily reduced to 45°.

The defect of the interventricular septum in the Eisenmenger complex is caused by the rotation of cushion B, which makes approximation of the proximal bulbar septum with the interventricular septum and the endocardial cushions impossible. The atypical coronary distribution is characteristic of various types of transposition; this has been thoroughly discussed by Spitzer.[15] The coarctation of the aorta, because of the accompanying anomalies, may be called the infantile type, and may be considered as part of the general hypoplasia of the aorta. This was also true in the case of Abbott.[3] A discussion of this coarctation is beyond the scope of this communication. The ductus arteriosus remained patent because of a difference in pressure between the pulmonary artery and the hypoplastic aorta.

The abnormal position of the left auricular appendage was a result of the abnormality in the absorption of the bulbus. Normally, during the second phase, the mesocardial (aortic) portion of the bulbus sinks into the auricular canal region, and thus the left auricular appendage comes to lie to the left of the aorta, and behind and to the left of the

pulmonary artery. The abnormal absorption of the bulbus in this heart, the rotation of cushion B ventrally, and the large size of the pulmonary artery displaced the auricular appendage to the right of both the aorta and the pulmonary artery.

It is of interest that, in most cases of Eisenmenger's complex, the aorta is a riding aorta. Ours was an exception, in that there was a partial transposition, or transposition type II of Spitzer (our type C). In this particular respect it is also of interest that in the case of Abbott[3] there was an aneurysm of the membranous septum. In a previous communication we[26] pointed out that in some (if not in all) cases of aneurysm of the membranous septum transposition is also present. The case of Abbott[3] bears out our original impression. This case was very similar to that of Eakin and Abbott[27] (transposition, infundibulum stenosis, and aneurysm of the membranous septum) (tetralogy of Fallot), except that in the case of Libman and Abbott there was no infundibular stenosis. Thus, both the tetralogy of Eisenmenger and that of Fallot may be classified according to types A, B, and C of our classification, in which A is transposition, with aneurysm of the membranous septum; B, transposition, with a riding aorta; and C, partial transposition, with the aorta and pulmonary artery arising from the right ventricle.

Our case differs from those already reported, in that, in addition to the congenital lesions, there was an old endocarditis, with stenosis of the mitral orifice. In the case of Abbott[3] there was also an old endocarditis of the mitral and aortic valves, but no stenosis was present.

The cause of death in cases of the Eisenmenger complex is usually heart failure, of which our patient died. The patients of Abbott[3] and Millman and Kornblum[9] died from subacute bacterial endocarditis.

SUMMARY

A case of the tetralogy of Eisenmenger is presented. The literature pertaining to this complex is reviewed, and the clinical differentiation of this anomaly from the tetralogy of Fallot is discussed. To explain this anomaly, a new theory of transposition is presented. The Eisenmenger complex is produced by an abnormality in the formation of bulbar ridge 3B. Instead of this ridge, the reptilian ridge 4B develops. The subsequent absorption of this abnormally formed bulbus proceeds in an abnormal fashion, causing both the aorta and pulmonary artery to arise from the right ventricle, as in our case, or producing a riding aorta with a septal defect, or a mild form of transposition with an aneurysm of the membranous septum.

REFERENCES

1. Abbott, M. E.: On the Differential Diagnosis of Congenital Cardiac Disease, Internat. Clin. **3:** 15, 1934.
2. Eisenmenger, V.: Die angeborenen Defecte der Kammerscheidewand des Herzens, Ztschr. f. klin. Med. (Suppl.) **32:** 1, 1897.

3. Abbott, M. E.: On the Incidence of Bacterial Inflammatory Processes in Cardiovascular Defects and on Malformed Semilunar Cusps, Ann. Clin. Med. 4: 189, 1925-26.

4. Abbott, M. E.: Osler's Modern Medicine, Philadelphia and New York, 1927, Lea & Febiger.

5. Baumgartner, E. A., and Abbott, M. E.: Interventricular Septal Defect With Dextroposition of the Aorta and Dilatation of the Pulmonary Artery (Eisenmenger Complex) Terminating by Cerebral Abscess, Am. J. M. Sc. 177: 639, 1929.

6. Stewart, H. L., and Crawford, B. L.: Congenital Heart Disease With Pulmonary Arteritis, Am. J. Path. 9: 637, 1933.

7. Rosedale, R. S.: Interventricular Septal Defect, Dextroposition of the Aorta, and Dilatation of the Pulmonary Artery, Am. J. Path. 11: 333, 1935.

8. Talley, J. E., and Fowler, K.: Tetralogy of Fallot (Eisenmenger Type) With Hypoplasia of the Dextroposed Aorta, Am. J. M. Sc. 191: 618, 1936.

9. Millman, S., and Kornblum, D.: Interventricular Septal Defect With Dextroposition of Aorta Without Stenosis of the Pulmonary Artery (Eisenmenger Complex) Complicated by Subacute Bacterial Endocarditis, J. Tech. Methods 15: 147, 1936.

10. Farre: On Malformations of the Human Heart, London, 1814. Quoted by Peacock.

11. Peacock, T. B.: Malformations of the Human Heart, London, 1866, John Churchill & Sons.

12. Fallot, A.: Contribution à l'Anatomie de la Maladie Bleue (Cyanose Cardiaque), Marseille méd. 25: 177, 138, 1888.

13. v. Schroetter, L.: See Eisenmenger.

14. Rokitansky, C. v.: Die Defecte der Scheidewände des Herzens, Vienna, 1875, W. Braumüller.

15. Spitzer, A.: Über den Bauplan des normalen und missbildeten Herzens, Virchows Arch. f. path. Anat. 243: 81, 1923.

16. Lev, M., and Saphir, O.: Transposition of the Large Vessels, J. Tech. Methods 17: 126, 1937.

17. Keith, A.: The Hunterian Lectures on Malformations of the Heart, Lancet 2: 359, 433, 519, 1909.

18. Pernkopf, E., and Wirtinger, W.: Die Transposition der Herzostien—ein Versuch der Erklärung dieser Erscheinung, Ztschr. f. Anat. u. Entwcklngsgesch. 100: 563, 1933.

19. Lev, M., and Saphir, O.: Truncus Arteriosus Communis Persistens. To be published.

20. Greil, quoted by Robertson, J. I.: The Comparative Anatomy of the Bulbus Cordis With Special Reference to the Abnormal Position of the Great Vessels in the Human Heart, J. Path. & Bact. 18: 191, 1913.

21. Fuchs: Quoted by Pernkopf and Wirtinger.

22. Benninghoff: Quoted by Pernkopf and Wirtinger.

23. Tandler, J.: Manual of Human Embryology, edited by Keibel, F., and Mall, F. P., vol. 2, Philadelphia and London, 1912, J. P. Lippincott Co.

24. Keith, A.: Schorstein Lecture on the Fate of the Bulbus Cordis in the Human Heart, Lancet 2: 1267, 1924.

25. Humphreys, E. M.: Truncus Arteriosus Communis Persistens, Arch. Path. 14: 671, 1932.

26. Lev, M., and Saphir, O.: Congenital Aneurysm of the Membranous Septum, Arch. Path. 25: 819, 1938.

27. Eakin, W. W., and Abbott, M. E.: Stenosis of the Pulmonary Conus at the Lower Bulbar Orifice (Conus a Separate Chamber) and Closed Interventricular Septum, With Two Illustrative Cases: Case 1, With Dextroposition of the Aorta and Aneurysm of Interventricular Septum, All Fetal Passages Closed; Case 2, With Patent Foramen Ovale and Subacute Infective Endocarditis, Am. J. M. Sc. 186: 860, 1933.

STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

I. Cutaneous Capillaries

J. Q. Griffith, Jr.,* M.D., E. Roberts, M.D.,
and H. O'Brien Corbit, A.M.
Philadelphia, Pa.

THE studies here being reported were undertaken with the hope of establishing certain objective criteria for the classification of hypertension. Such a classification would be of value only if more than one disease entity is represented among the cases of hypertension. It seems probable that such is the case. Indeed, using two objective criteria, i.e., eye-ground examination and muscle biopsy, Keith, Wagener, and Kernohan[1] were able to segregate a form of malignant hypertension which pursued a fairly typical course.

The capillaries of the skin can be readily examined under the microscope, and, in many instances, the blood flow visualized. Cutaneous capillaries which are located in parts not protected by clothing are constantly open. Lewis,[2] who studied the back of the hand, concluded that all capillaries that can open are always open. That this is not true for protected areas was shown by Bordley, Grow, and Sherman,[3] and by Roberts and Griffith.[4] A convenient way to secure maximal capillary dilatation is to make a needle prick through a drop of 1:1,000 solution of histamine near the area under observation, so that this area lies within the flare. It was planned to carry out such studies in a series of patients with high blood pressure and to express the results as quantitatively as possible. The establishment of certain normal standards was therefore required.

MATERIAL AND METHOD

Persons used as normal controls were, for the most part, patients from the surgical wards who were hospitalized for elective operations. Such persons were ambulatory, afebrile, and without evidence of cardiovascular disease or diabetes. None had recently undergone surgical procedures. The period of the study was the winter of 1938-39 and the spring of 1939. All subjects had been hospitalized at least twenty-four hours before the studies were begun.

In general, the procedure was as follows: At 9 A.M. the subject came to the laboratory after breakfast, but without having been outdoors. Two circular areas were marked with an inked die on the extensor area of each forearm above the line of the cuff, i.e., in an area normally protected by clothing. The area enclosed in each circle was approximately 3.1 sq. mm., but, because of differences in the spread of the ink particles, this area varied slightly; the variation, however, probably never exceeded 5 per cent. Capillaries were then counted in this area, using an Ultrapak and the technique previously described by Roberts and Griffith.[4] The results, by

calculation, were expressed in terms of capillaries per square centimeter. Corn plasters were then placed over the marks to protect them. At 4 P.M. of the same day the subjects returned to the laboratory and the capillaries in two of the four areas were again counted. At 9 A.M. the following day counts were made in the same two areas as on the previous afternoon; histamine was then pricked into the skin near all four of the marked areas, and counts were made again. If, for any reason, the ink markings on the skin showed any blurring, as from rubbing or washing by the subject, counts from that area were discarded.

Patients with hypertension* were selected from the wards and dispensaries of the University Hospital and from the private practices of the authors. As a further control, other patients without hypertension, but of about the same age, were chosen from the same wards and dispensaries and examined similarly. Most of these patients had some form of cardiovascular disease or diabetes, and might be designated "abnormal" controls, as contrasted with the normal controls previously described. Many of the dispensary patients had been in the hospital only an hour when the studies were made. Sometimes the die was used and counts made by the same technique employed for the normal controls. More often the inked circle was omitted, and an entire microscopic field observed. This, roughly, equalled about four of the marked circles. Under such circumstances the absolute figures are only approximate, but the percentage of increase may be estimated with fair accuracy. Although this modification saved time and histamine pricks, after much experience it became clear that the more exact method, using the die, is preferable.

RESULTS

A. On the normal controls. The absolute figures for capillaries per square centimeter show considerable variation. The number which were open initially ranged from 100 to 1,300 per square centimeter, but most of the figures lay between 200 and 600, as shown in Fig. 1A. Counts per square centimeter after the injection of histamine varied from 250 to 1,300 and showed a little more spread, but for the most part ranged between 500 and 900, as shown in Fig. 1B. There was no significant variation with sex or age, although it should be noted that the young adult and middle-aged subjects predominated in this series. Fig. 1C and 1D show that, as a rule, more capillaries were open at the end than at the beginning of the twenty-four-hour period of observation. This may have been caused by slight irritation from the corn plasters, although we could find nothing less irritating to the skin. The number of subjects with more capillaries open on the second morning was to the number with more capillaries open on the first morning as 4 is to 3; the number of subjects with more capillaries open on the first afternoon was to the number with more open on the first morning as a little more than 3 is to 1.

Fig. 2A shows the difference in counts on the same person in different areas on the forearm, with the highest count plotted against the lowest. The average difference was 224 capillaries per square centimeter, and

the range, from 40 to 600.   Fig. 2*B* shows the same difference after the
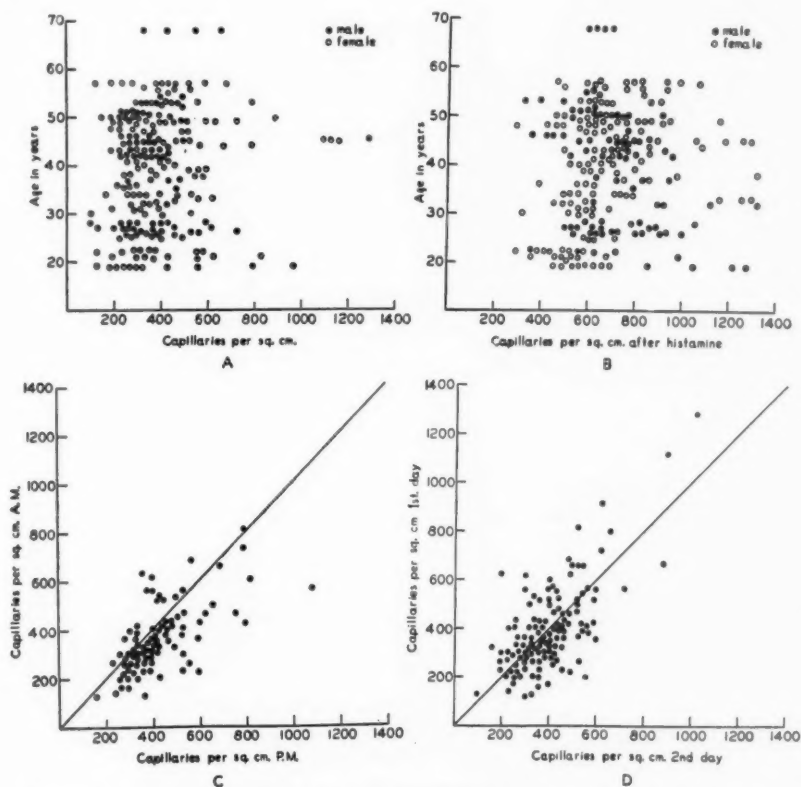injection of histamine; the range was from 20 to 620, and the average,
220.

Fig. 1.—*A*, Capillary counts on normal men and women of varying ages. *B*, Capillary counts on normal men and women of varying ages, made in areas included in a
histamine flare.   The persons and the areas counted are the same as in *A*.   *C*,
Capillary counts on the same areas, made in the morning and again late in the afternoon, on normal men and women. *D*, Capillary counts on the same areas, made on two
successive mornings on normal men and women.

Fig. 2*C* compares the number of capillaries open before the injection
of histamine with the number open after giving histamine, in actual
figures per square centimeter.   If the number open after injecting
histamine be taken as 100 per cent, an average of almost exactly
50 per cent were open before giving histamine, although the range
was from 20 to 90.   In two-thirds of the areas counted, 51 per cent,
or more, of the total number of capillaries were open before giving
histamine, and in only one-third 50 per cent, or less, before giving
histamine.   However, in three-fourths of the areas counted, 40 to 70
per cent of the capillaries were open before injecting histamine, and the
remaining fourth was divided almost equally between areas with 70 to
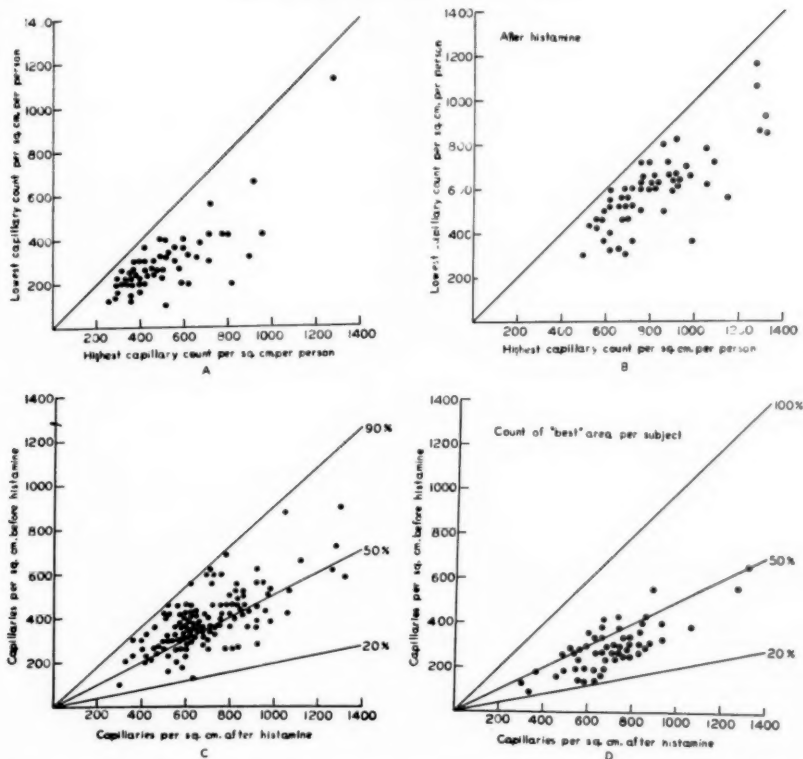90 per cent, and areas with 20 to 40 per cent, of their total number of

Fig. 2.—*A*, Chart intended to show the maximum variation in capillary counts on different areas of the forearm on the same normal subject. Each dot represents one subject. *B*, Same as *A*, except that maximal local dilatation had been produced by injecting a drop of 1:1000 solution of histamine. *C*, Capillary counts on the same areas on normal persons, made before and after injecting histamine locally. For details, see text. *D*, Same as *C*, except that only one area per subject is charted, and the area chosen was that one of the four in which the smallest per cent of the total number of capillaries were open before histamine. For details, see text.
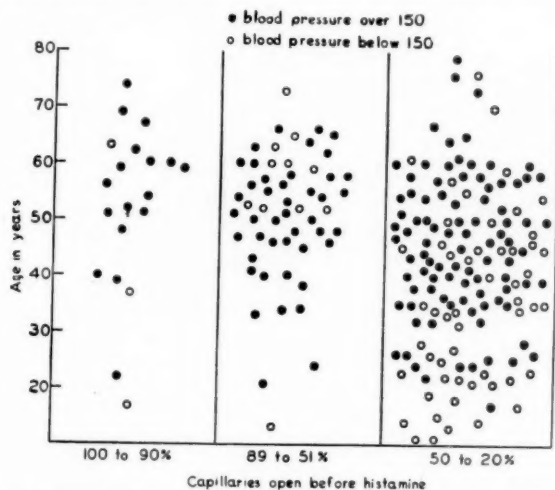

Fig. 3.—Chart showing per cent of capillaries open before injecting histamine in persons with cardiovascular disease, including hypertension. The count after injecting histamine is considered to be 100 per cent. For details, see text.

capillaries initially open. The results are charted somewhat differently in Fig. 2*D*, in which only one area per person is graphed, and that is the area which had the lowest per cent of total number of capillaries before the injection of histamine. Thus, in this series of normal subjects, every person had at least one count that showed that not more than 62 per cent of the total number of capillaries were open, and four-fifths of the subjects had at least one count below 50 per cent.

B. On patients. Some had hypertension and others did not. The non-hypertensive patients usually had, as previously stated, some form of cardiovascular disease or diabetes, and were not considered normal. Fig. 3 shows the results of studies on 221 such persons, including 156 hypertensive and sixty-five nonhypertensive subjects. Arbitrary divisions were made as follows: (1) Those with 90 to 100 per cent of their capillaries open before the injection of histamine were considered to have diminished capillary mobility. (2) Those with 51 to 89 per cent of their capillaries open before the injection of histamine were considered to have moderate capillary mobility. (3) Those with 50 per cent, or less, of their capillaries open before the injection of histamine were considered to have high capillary mobility. The group with diminished capillary mobility was regarded as definitely abnormal, whereas that with high capillary mobility was considered normal. The middle group, with moderate capillary mobility, was regarded as uncertain; it included some persons who were normal and others who were probably abnormal. It will be seen that 146 subjects fell within the third group, of which ninety-four had hypertension and fifty-two did not. Twenty were included in the first group, which was definitely abnormal; only three of these patients did not have hypertension. The remaining fifty-five, of whom eleven did not have hypertension, fell in the intermediate group. There was no definite relationship between age and grouping.

<div align="center">DISCUSSION</div>

Organic capillary changes of a degenerative sort are difficult, if not impossible, to diagnose with methods now available. Even "acute capillaritis," characterized by capillary hemorrhages or "sticking" of leucocytes, is difficult to recognize on histologic section. That some organic change did exist in certain of the cases just reported might be conjectured, at least in the group with diminished, and perhaps some with moderate, capillary mobility. Direct evidence is, however, lacking.

It is probable that many persons with diminished capillary mobility have, in addition, an absolute diminution in number of capillaries. Not enough data have been collected to make this a certainty, but it was more difficult to find fields which were "suitable for observation" in these patients than in normal subjects. The areas which were finally selected for study were chosen only after examining several fields and were

probably above the average in vascularity. The significance of this was not recognized until the study was nearly completed.

It may be difficult or impossible, in certain cases, to differentiate between diminished or moderate capillary mobility and an initial vascular dilatation, such as that which occurs after exposure to sun and wind, in hyperthyroidism, with fever, and in certain skin diseases. The percentile changes may be similar, but other factors aid in differentiation: (1a) If there is initial vascular dilatation caused by exposure to sun and weather, a history of such exposure should be obtainable. The arm may appear weather-beaten. The total count, both before and after giving histamine, is within the normal or high normal range. Branches of the subpapillary venous plexus are usually visible. (1b) By contrast, if the condition is the result of diminished capillary mobility, there is no history of exposure, the arm appears pale, the total count is usually a low normal or below normal, and few, if any, branches of the subpapillary venous plexus are visible. (2) With systemic conditions which lead to vascular dilatation, as hyperthyroidism or fever, there is evidence of the underlying condition. (3) The presence of a skin disease is usually obvious.

Theoretically, an area which is subject to even less exposure than the forearm might be preferred. The upper arm could be used, but this would be much less convenient and open to many of the same objections as the use of the forearm. The face is an exposed area like the hand, and, moreover, the subpapillary venous plexus is always large and dilated, thus interfering with observation of the capillaries. Use of the chest and abdomen is impracticable because respiratory movement makes careful capillary observation impossible. The legs and feet are available, but here the vessels are affected by hydrostatic pressure, and a defective vein could cause more local effects than would systemic disease. We consider the forearm and upper arm the areas most suitable for this type of study.

SUMMARY

Capillary counts on the forearm were made on normal persons and on patients with various diseases, especially hypertension. The initial counts were compared with counts made during histamine dilatation; the latter were thought to indicate the total number of capillaries present. It was found that average counts on normal persons showed that 50 per cent of the total number of capillaries were open initially, and, if areas of adequate size were counted, at least one area would show no more than 62 per cent open initially. In certain pathologic vascular states, the initial counts approached or equalled the total counts. After persons with a local or systemic cause for initial dilatation were excluded, the capillary mobility of the remainder was graded as follows: (1) 50 per cent, or less, of total capillaries open initially, high capillary mobility;

(2) 51 to 89 per cent of capillaries open initially, moderate capillary mobility; (3) 90 to 100 per cent of capillaries open initially, diminished capillary mobility. Although most of the persons with hypertension fell into the first, or normal, group, approximately 40 per cent were found to belong in the groups in which there was diminished or moderate capillary mobility. None of the normal controls fell into the group in which mobility was diminished, and, if adequate areas were counted, four-fifths of them showed high capillary mobility.

REFERENCES

1. Keith, N. M., Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41:** 141, 1928.
2. Lewis, T.: Regulation of Blood Flow Through Capillaries of Human Skin, Heart **13:** 1, 1926.
3. Bordley, J., Grow, M. H., and Sherman, W. B.: Intermittent Blood Flow in Capillaries of Human Skin, J. Clin. Investigation **14:** 702, 1935.
4. Roberts, E., and Griffith, J. Q., Jr.: A Quantitative Study of Cutaneous Capillaries in Hyperthyroidism, AM. HEART J. **14:** 598, 1937.

STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

II. Minute Vessel Pressure

J. Q. Griffith, Jr.,* M.D., E. Roberts, M.D.,
and H. O'Brien Corbit, A.M.
Philadelphia, Pa.

NUMEROUS methods have been devised for measuring pressure in cutaneous capillaries. The subject has been reviewed by Eichna and Bordley.[1] Indirect methods, such as those described by Danzer and Hooker,[2] and by Kylin,[3] can be used clinically, but the results obtained are unreliable. On the other hand, the direct method of Landis,[4] while admittedly accurate, presents such technical difficulties as to virtually preclude its clinical use. With Landis'[4] method, the pressure is measured without interrupting capillary flow. It should be noted that the indirect methods produce capillary block, with cessation of flow. The method employed in these studies was an indirect one that has been evolved during the past ten years from the Danzer-Hooker method.

DESCRIPTION OF THE APPARATUS

The apparatus is composed essentially of the following parts:

1. A microscope with Ultrapak attachment and objective for capillary observation.

2. A compression chamber, transparent through the center, with appropriate attachments for exerting a measured pressure on the skin surface.

The following description should be read with the help of Fig. 1.

An ordinary microscope (A), with stage detached, may be used. The usual objective-changing device, with the objectives, is removed, and replaced by an Ultrapak (B), with special Ultrapak objective (65 X Leitz-Wetzlar). A 10 X ocular of the ordinary type may be used. The Ultrapak is connected (C) to the house current through a rheostat, which must be adapted to the type of current available. The microscope is focused in the usual manner.

The compression chamber (E) consists of an upper and lower part. The upper part is made of metal, and supports a central disc of optical glass (D). One margin is pierced by a metallic tube which connects the chamber with the oil system. At an opposite point on the margin, an outflow screw (not shown), when loosened, permits air and oil to escape and is useful in getting rid of bubbles when the chamber is being filled. The lower part of the compression chamber (E) consists of a metal ring which supports a cellophane membrane (F). The compression chamber is held on a rod support (H) which is moved by a micromanipulator (I) (indicated, but not shown). The metal tube leading from chamber E is connected by koroseal† tubing to a three-way stopcock (K). Koroseal is nearly as flexible as rubber and does not rot when left in contact with oil. The three-way stopcock connects with a reservoir for oil (L) and a glass side arm (M). This side arm (M)

is connected by ordinary rubber tubing (*R*) and a Y-tube (*N*) with a mercury manometer (*O*) and a rubber bulb (*P*) which can be compressed by turning a thumb screw in box *Q*.

DESCRIPTION OF THE METHOD

Reservoir *L* is partly filled with mineral oil, with stopcock *K* in a neutral position. The escape screw on the upper margin of the compression chamber (*E*) is then loosened, and the chamber tilted slightly so that the screw is uppermost. Stopcock *K* is then turned so that the reservoir is connected only with the compression chamber (*E*), and oil is permitted to flow until all of the air has been expelled from the chamber, after which the chamber is closed by tightening the escape screw. If necessary, more oil may be added to the reservoir (*L*). Then stopcock *K* is turned so that reservoir *L* is connected with the side arm (*M*), and an interval allowed for the oil to rise in the side arm (*M*) to the same level as in the reservoir. Stopcock *K* is then turned as illustrated in Fig. 1, with the chamber (*E*) connected with the pressure system (*OPQ*) and the reservoir disconnected.
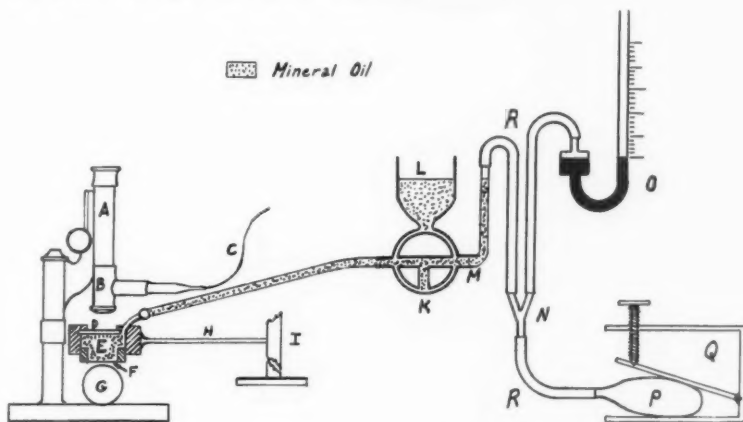

Fig. 1.—Diagram of apparatus for measuring minute vessel pressure. For details, see text.

The measurement is made with the subject seated beside a table, on which the apparatus is placed. When the arm is in position, the area selected for observation is about at the level of the middle of the sternum. An area on the extensor surface of the forearm, a few inches below the elbow, is chosen. The flexor surface may be used, but is less desirable because the greater prominence of its subpapillary venous plexus makes capillary observation more difficult. Excessively long hair may be removed by scissors or clippers, but the skin surface must not be scraped. The area to be studied is sometimes marked in ink with a die. The skin is moistened with mineral oil, and the arm is placed in position under the microscope. The position of the arm is indicated (*G*) in Fig. 1.

The chamber (*E*) is lowered by the micromanipulator (*I*) until the cellophane membrane (*F*) makes contact with the skin surface, but without exerting any appreciable pressure on it. In Fig. 1, for greater ease in illustration, the chamber (*E*) appears larger than it need be in relation to the size of the arm. The cellophane membrane may be no more than 1.5 inches in diameter. The capillaries are then visualized through the microscope and watched continuously while the thumb screw on box *Q* is turned, compressing bulb *P*, and raising the pressure in chamber *E*, as shown on manometer *O*. When the capillaries disappear, the manometer reading is recorded.

Special Precautions.—1. The cellophane membrane. The attachment of the
cellophane membrane to its holder must be loose enough to allow it to bulge slightly
downward when the pressure in the chamber is raised. This bulge must be sufficient
to permit pressure in the chamber (*E*) to be transmitted to the skin. If the mem-
brane is too tight, or if the pressure measurement is begun with the membrane too
far from the skin, the capillaries will not disappear, regardless of the amount of
pressure applied. Conversely, if the chamber is lowered too far the cellophane itself
will make pressure on the skin, which may obliterate capillaries even before the
pressure in the chamber is raised. Making this adjustment requires some experience,
but, in general, if the capillaries are readily visible before the measurement and dis-
appear at a certain point when pressure is raised, one may feel confident that the
height of the chamber was correct.

2. Oil leakage. Some leakage of oil always occurs around, and possibly through,
the cellophane. Therefore, during the course of the measurement, the level of the oil
in the side arm (*M*) falls somewhat, and the loss must be made up by connecting
with the reservoir before the next determination. The oil level in the side arm (*M*)
should never be permitted to fall to the level of the stopcock; if it does, air bubbles
will get into the oil system. If they reach the koroseal tube or even the chamber (*E*),
they should be expelled by opening the escape screw in chamber *E* and letting the
oil run through from the reservoir.

Test of the Method.—As a rule, readings can be duplicated by the same observer
within 2 mm. of mercury, and by two observers within 3 mm. of mercury. However,
such duplication does not bear directly upon the question of the accuracy of the
method.   Theoretically, raising venous pressure should raise capillary pressure.
Venous pressure can be raised by inflating a blood pressure cuff about the arm.
After a period of adjustment, venous pressure should equal cuff pressure. Eichna and
Bordley[1] were unable to obtain graded rises in capillary pressure, as measured by
the Danzer-Hooker method, to correspond with increments of cuff pressure. When
they used the method of Landis, corresponding rises of capillary pressure were
obtained. They concluded that the Danzer-Hooker method was unreliable. The cuff
they used was of the usual type which is employed for measuring arterial pressure.
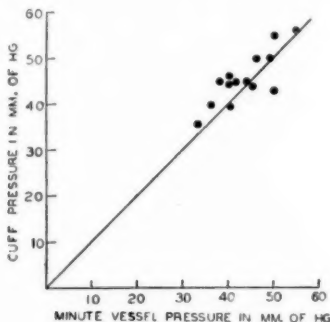

Fig. 2.--Chart intended to show the correlation between artificially elevated venous
pressure, produced by inflating a blood pressure cuff about the upper arm, and minute
vessel pressure. In every instance the initial minute vessel pressure was 23 mm. of
mercury, or lower. For details, see text.

On fifteen different persons, all with initial minute vessel pressures below 23
mm. of mercury, the following procedure was used. One person placed an extra
large (5.5 × 20 inches) blood pressure cuff about the upper arm of the subject and
inflated it to a pressure unknown to the person reading the minute vessel pressure,
which was measured in the usual way on the forearm. In two to four minutes, or

after the minute vessel pressure became constant, the reading was taken, and the results were charted (Fig. 2). Repeated observations on the same subject were considered unwise because of the hyperemia and edema which made it difficult to distinguish capillaries from branches of the subpapillary venous plexus. It will be seen that the minute vessel pressure rose to approximately the same level as the venous pressure. It did not regularly exceed venous pressure, as was the case when it was measured by Landis[4] and Eichna and Bordley[1] by the method of Landis.[4]

Comparison With the Method of Danzer and Hooker.[2]—1. The forearm is used instead of the finger because (a), as was shown in Part I, changes in the number of open capillaries may occur in the forearm, but not in the hand or finger. The forearm might therefore be expected to reflect systemic changes better, whereas the hand responds maximally to local conditions. (b) The arteriolar and venous limbs of the capillaries pass at right angles to the surface in the forearm, but run parallel to it in the nail bed. Therefore, when pressure is applied to them in the forearm, they empty, but in the nail bed they usually do not.

2. The chamber is maneuvered with a micromanipulator.

3. The chamber is filled with mineral oil instead of air, to improve visibility.

4. A microscope with Ultrapak attachment is used.

5. The end point is disappearance of capillaries. Flow is not observed.

6. The pressure measured is thought to be minute vessel pressure, not capillary pressure. Reasons for this will be discussed later.

Clinical Material.—Patients with and without hypertension were chosen from the wards and dispensaries of the hospital of the University of Pennsylvania. Minute vessel pressure was measured by the method just described. Histamine (1:1,000 solution) was then injected into the adjacent skin, and, when the flare area included the area under observation, the measurement was repeated. Many of the same patients from whom data were obtained for Fig. 3 of Part I were studied.

RESULTS

Minute vessel pressure is plotted against systolic blood pressure in Fig. 3A, and against diastolic blood pressure in Fig. 3B. Each dot represents a measurement on a different subject. The patients were unselected, except that persons with skin rashes and other local cutaneous lesions were excluded. It will be seen that minute vessel pressure never exceeded 25 mm. of mercury until systolic pressure rose above 140, and diastolic pressure above 90. No considerable number of subjects had minute vessel pressures above 25 until the systolic blood pressure exceeded 160, and the diastolic pressure, 100. Above these levels, some hypertensive patients had elevated minute vessel pressures and some did not. However, in the few cases in which the systolic blood pressure was above 250 and the diastolic above 150, minute vessel pressure was uniformly elevated.

As a rule, histamine causes a change in minute vessel pressure. In Fig. 4, such changes are plotted against per cent changes in capillary count. As many of the capillary counts were only approximate, there is a tendency toward clustering near the round numbers. A minute vessel pressure change of 3 mm., or less, was considered within the limit of error of the method, and, therefore, as insignificant. Capillary counts were grouped according to whether the mobility was diminished,
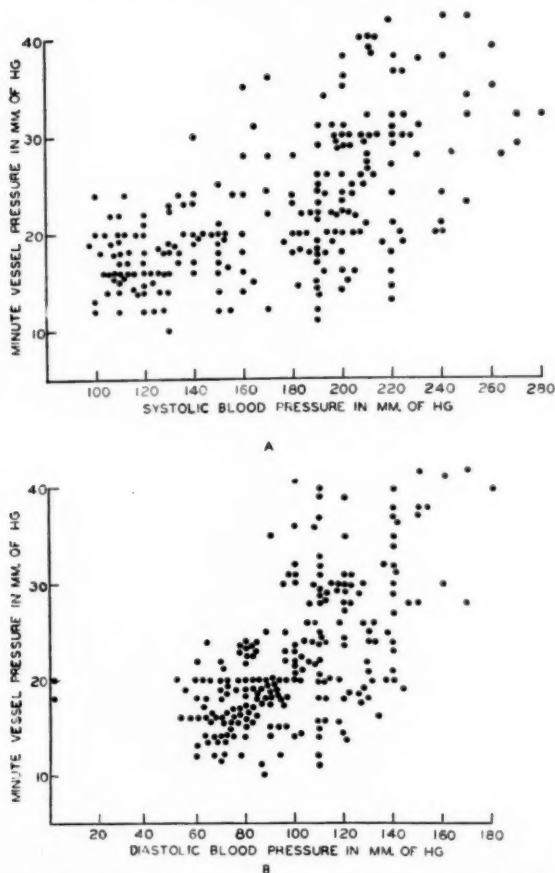
Fig. 3.—*A*, Chart showing relation of minute vessel pressure to systolic blood pressure. *B*, Chart showing relation of minute vessel pressure to diastolic blood pressure.
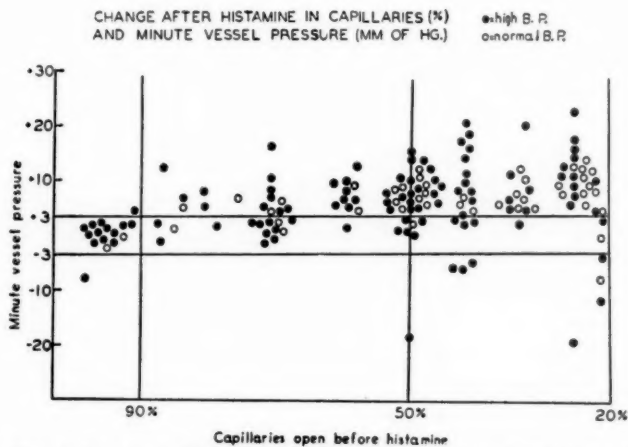

Fig. 4.—Chart showing relation of change in minute vessel pressure after the injection of histamine to "capillary mobility," as defined in Part I. For details, see text.

moderate, or high, as described in Part I. It is apparent that sixteen persons had diminished capillary mobility, and that fourteen of these showed no significant change in minute vessel pressure. Certain persons with moderate and high capillary mobility also showed no significant change in minute vessel pressure, but the proportion was lower. An increase of 13 mm. of mercury, or more, occurred only in subjects with hypertension. Nine persons showed a significant fall in minute vessel pressure. This is difficult to explain, but all of these patients were among those who were studied during the early part of the investigation. None such have been seen in the past year. It is suggested, therefore, that this apparent fall in pressure represented a technical error.

DISCUSSION

It appears that minute vessel pressure, as measured by this method, approximately equals venous pressure when the latter is elevated by means of a cuff. It should be noted, however, that this was true only when the extra large cuff was used. True capillary pressure, as measured by the method of Landis,[4] and as applied by Landis[4] and Eichna and Bordley,[1] rises under similar circumstances to a point 8 mm., or more, above venous or cuff pressure. Therefore, the method satisfies the postulates of Eichna and Bordley in one respect, but not in another: (1) It shows that an elevated minute vessel pressure is quantitatively associated with an elevated venous pressure. (2) The minute vessel pressure tends to equal, but not to exceed, venous pressure.

It may be that figures obtained by the indirect method should be considered of relative, rather than of absolute, significance. Skin elasticity and resistance may interpose a tangible, but fairly constant, factor. Moreover, it is not certain exactly what pressure is being measured. Comparison may be made with the actual figures obtained by Landis.[4] The pressures he obtained in normal subjects were as follows: (1) In the arteriolar limb, an average pressure of 32 mm. of mercury, with a range of 21 to 48; (2) at the summit of the loop, an average pressure of 20 mm., with a range of 15 to 32; (3) in the venous limb, an average pressure of 12 mm., with a range of 6 to 18. Thus, as far as actual figures are concerned, the pressures obtained by the indirect method correspond more nearly with those obtained by Landis at the summit of the loop than in the arteriolar limb. Moreover, by the indirect method, it is the summit of the loop that is observed, and this is where the measurement is made.

Nevertheless, for the following reasons, it appears probable that the pressure actually measured by the indirect method varies with the pressure in the precapillary arteriole. The pressure required to block

a capillary in which blood has been flowing is greater than the normal pressure in that capillary while flow is continuing. As the capillary is blocked, the pressure recorded is that at the nearest unblocked branch on the arterial side, i.e., probably the pressure in the precapillary arteriole. This possibility appears to have been insufficiently recognized by other workers. To take an extreme example as an illustration, if it were possible to block all of the capillaries in the body simultaneously, and if the arterial system were entirely rigid, the pressure required to produce the obstruction would be approximately aortic pressure. The pressure required to block one branch of a Y-branching vessel is not the pressure which is normally present at that point under conditions of flow, but rather the pressure at the fork of the Y where a collateral branch is open.

The pressure required to empty a capillary in which there is no flow is the pressure just in excess of that in the subpapillary venous plexus. This, theoretically, should be somewhat less than that required to block the inflow from the arterial side (i.e., by the difference between the pressure in the subpapillary venules and the subpapillary arterioles). Under such circumstances, one would expect some of the capillaries to disappear at one pressure level, and some at a slightly higher pressure, and the latter would include those capillaries in which flow was present. Actually, a pressure change of less than 1 to 2 mm. is all that is required to obliterate all of the capillaries after the first ones have disappeared. A possible explanation is that the pressure that empties the capillaries also blocks the subpapillary venous plexus, which must be connected with the precapillary arteriolar plexus either through capillaries or arteriovenous anastomoses. Thus, in either case, the actual pressure which is measured is that in the precapillary arteriole; it is certainly not true capillary pressure, and the term "minute vessel pressure" is preferable.

Minute vessel pressure does not exceed 25 mm. of mercury in persons whose arterial blood pressure is normal. Persons with elevated blood pressure can be divided into two groups: (1) those with normal minute vessel pressure, and (2) those with elevated minute vessel pressure. As a rule, after the injection of histamine the pressure rises or remains the same. There is a tendency for persons with diminished capillary mobility to have an insignificant change in minute vessel pressure after histamine is given. It is suggested that in such cases there may be sclerosis of the precapillary arteriole.

In normal persons with high or moderate capillary mobility and without hypertension, minute vessel pressure may rise 3 to 13 mm. of mercury after histamine is given. Under similar conditions, some patients with hypertension will show a rise in minute vessel pressure of more than 13 mm. of mercury. In such cases it is possible that arteriolar spasm may be unusually marked.

SUMMARY

An indirect method for measuring the pressure in the minute vessels of the skin is described. Although the reading is made by inspecting the capillaries, the pressure measured is probably that in the precapillary arteriole. In normal persons the pressure which is measured in this way does not exceed 25 mm. of mercury and will increase 3 to 13 mm. of mercury in the flare area of a histamine wheal. In persons with hypertension the initial minute vessel pressure may be normal or elevated, and, in the area of a histamine flare, it may fail to change, show a normal rise, or show an exaggerated rise of more than 13 mm. of mercury. When the change is less than 3 mm. of mercury, whether or not the subject has hypertension, it is suggested that sclerosis of the precapillary arteriole is present.

REFERENCES

1. Eichna, L. W., and Bordley, J.: Capillary Pressure in Man, J. Clin. Investigation 18: 695, 1939.
2. Danzer, C. S., and Hooker, D. R.: Determination of Capillary Blood Pressure in Man With the Microcapillary Tonometer, Am. J. Physiol. 52: 136, 1920.
3. Kylin, E.: Clinical Determination of Capillary Tension, Acta med. Scandinav. 57: 566, 1923.
4 Landis, E. M.: Microinjection Studies of Capillary Blood Pressure in Human Skin, Heart 15: 209, 1930.

STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

III. Cutaneous Lymphatic Flow

J. Q. Griffith, Jr.,* M.D., E. Roberts, M.D., R. B. Rutherford, M.D., and H. O'Brien Corbit, A.M.

Philadelphia, Pa.

LANDIS[1, 2] has shown that the rate at which fluid leaves the capillaries varies directly with the pressure in the capillaries and inversely with the colloid osmotic pressure of the plasma. It is probable that, when flow is unobstructed, capillary pressure never gets very high because of the rapid loss of fluid. However, if capillary pressure is raised by obstruction of venous outflow (resulting from defective valves, varicosities, etc.), the loss of fluid from the capillary may not be very great, because, as some fluid is lost, the blood colloids become concentrated, and, locally, the colloid osmotic pressure rises. A pathologic change in the endothelium of the capillaries may make them partially permeable to blood colloids, thus lowering colloid osmotic pressure and increasing fluid loss from the capillaries. It is possible, but has not been proved, that such increased loss of fluid may occur even without loss of protein. Again, when gross edema is present, tissue pressure may be raised sufficiently to interfere with loss of fluid through the capillaries. Part of the fluid that leaves the capillaries is reabsorbed into the capillaries, and the remainder passes into the lymphatic system.

While the processes of fluid interchange are admittedly complex, in general it may be assumed that, in the absence of edema and with unobstructed lymphatic vessels, the rate of lymphatic flow should vary directly with the rate at which fluid leaves the capillaries. To avoid artifacts produced by local hyperemia and muscle movements, the part being tested should be at rest. By means of the method of McMaster,[3, 4] it was decided to measure the rate of cutaneous lymphatic flow in a series of persons, and compare the results with measurements of blood pressure and minute vessel pressure.

METHOD

The dye used was patent blue; it was prepared by the method of McMaster.[3] An attempt was made to see that the subject did not use his arm strenuously for some time prior to the test, although absolute inactivity was considered undesirable. As a rule, the patient was under observation in the laboratory for a half hour before the test was performed. No previous constriction of the arm was permitted, as by a tourniquet or blood pressure cuff. With the patient seated and the forearm motion-

less on a table before him, approximately 0.03 c.c. of the patent blue solution was injected intracutaneously in the flexor surface of the forearm. After the injection the blue area so outlined was traced on nonwaterproof cellophane with ink and an ordinary fountain pen. Subsequent tracings were made every five minutes for a period of twenty minutes. Attention was paid, not to the size of the initial area injected, but to its increase in size and the extent of its streamers. The final appearance consisted of (1) a central, homogeneously dark-blue area which sometimes spread during the period of observation; (2) a darkly stained web adjacent to the central blue area; (3) a light-blue streamer or streamers extending upward 0.5 to 10 cm. from the central area. The adjacent, deeply stained web probably represents lymphatic vessels directly injected with the dye, and the light-blue streamers probably represent lymphatic spread. Judgment as to cutaneous lymphatic flow is based upon the extent of the streamers, and a distinction is made between normal and increased lymph flow.

Fig. 1.—*A*, Chart showing relation between systolic blood pressure, minute vessel pressure, and cutaneous lymph flow in patients, many of whom had cardiovascular disease. *B*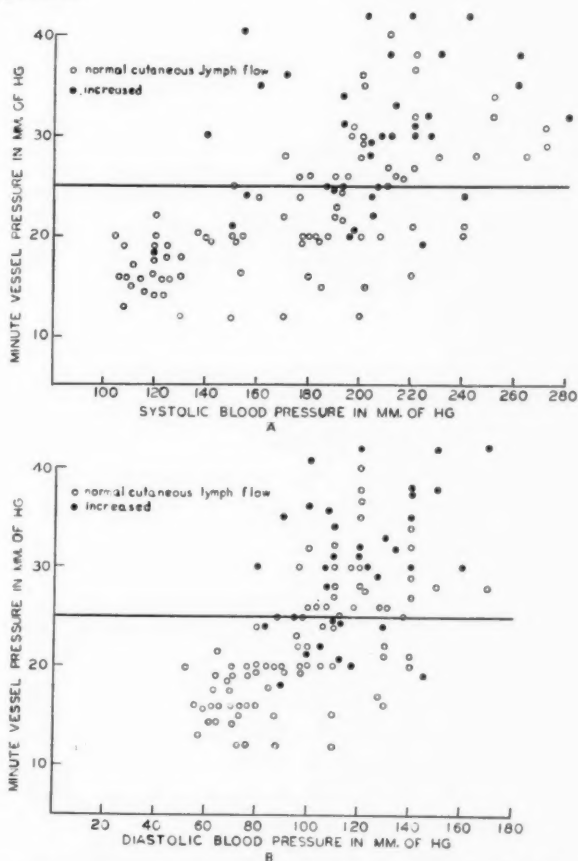, Chart showing relation between diastolic blood pressure, minute vessel pressure, and cutaneous lymph flow in patients, many of whom had cardiovascular disease.

Minute vessel pressure was measured as described in Part II, and it will be seen (Figs. 1*A* and *B*) that many of the same patients were studied again, but this time with reference to their cutaneous lymphatic flow, as well.

A few experiments were carried out on rats in order to clarify certain phases of the relation between minute vessel pressure and cutaneous lymphatic flow. The details of these experiments will be given in Part V; suffice it to say here that if rats are given water by mouth in an amount equivalent to 5 per cent of their body weight, together with an antidiuretic dose of pitressin intraperitoneally, some of them will develop vascular hypertension within 1.5 hours. In Fig. 2 the results of
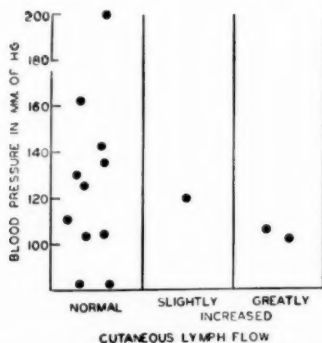

Fig. 2.—Chart showing relation between cutaneous lymph flow and blood pressure in rats which received water by mouth in an amount equivalent to 5 per cent of their body weight, together with an antidiuretic dose of pitressin, intraperitoneally.

measuring cutaneous lymphatic flow and blood pressure in such animals are recorded. Blood pressure was measured by the indirect method of Griffith, and cutaneous lymphatic flow by the patent blue method, in the skin of the lateral abdominal wall. Ether anesthesia was used only when it was necessary to measure the blood pressure and the lymphatic flow.

RESULTS

It is seen in Figs. 1 *A* and *B* that cutaneous lymphatic flow was increased in thirty-six persons. The minute vessel pressure was below 25 mm. of mercury in eleven of these patients, and above in twenty-five. Of the thirty-six persons, thirty-five had systolic blood pressures of 140, or over, and thirty-four had diastolic pressures of 90, or over. Many persons with equally high or higher blood pressures had a normal cutaneous lymphatic flow. Plasma protein estimations were made in some instances, but not in all, so that we do not have enough data to say whether, in general, the subjects with increased lymphatic flow and low minute vessel pressure did or did not have a normal plasma protein in all cases. The protein content of the plasma in a few such cases was normal.

Fig. 2 shows the results of the rat experiments. Hypertension in these animals under such experimental conditions is associated with an increased blood volume caused by failure to eliminate fluid properly. Since the dosage of pitressin was minimal, not all of the animals showed the antidiuretic effect and hypertension. It was anticipated that the hypertensive animals would have an increased lymphatic flow. In fact, the three animals with increased lymphatic flow had normal blood

pressures, whereas the three with high blood pressures had normal cutaneous lymphatic flow.

Discussion of certain theoretical relations between minute vessel pressure and cutaneous lymphatic flow will be deferred until after the presentation of data dealing with blood volume, in Part IV. However, at this time two questions will be considered.

If the minute vessel pressure which is measured is actually the pressure in the precapillary arteriole, then it does not differentiate between cases in which an increased vascular pressure extends through to the capillaries and others in which, in spite of an increase in arteriolar pressure, the arteriolar constriction is sufficient to prevent the excess of pressure reaching the capillaries. It is suggested that measuring both minute vessel pressure and cutaneous lymphatic flow makes such a differentiation possible, at least presumptively. A subject with increased cutaneous lymphatic flow and a normal colloid osmotic pressure may be regarded as having at least a slightly elevated capillary pressure. The cause might be local or systemic. If the person has, in addition, vascular hypertension and an elevated minute vessel pressure, it may be considered that the capillary hypertension is a part of the general vascular hypertension. On the other hand, if a subject has high blood pressure and elevated minute vessel pressure, but a normal cutaneous lymphatic flow, it may be that arteriolar constriction has spared the capillaries and tissues from the effects of the elevated arterial pressure.

In a recent study of cutaneous lymphatic flow, by means of patent blue or some other colloidal blue dye, in the excised ear of the rabbit, Parsons and McMaster[5, 6] showed that the rate of lymphatic flow was much greater with a pulsating perfusion pressure than with a constant pressure. They therefore suggested that it was the pulsation of the arteries themselves which, in certain patients with nephritis without arteriosclerosis, caused an increase in cutaneous lymphatic flow. Persons with sclerotic vessels, on the contrary, would have a diminished rate of lymphatic flow. If this explanation were true, one might expect that young persons with aortic regurgitation would have an increased cutaneous lymphatic flow. However, four such patients have been studied, all under 25 years of age, with diastolic pressures of zero, as measured in the usual auscultatory manner, and the flow was normal in every case. In what other way McMaster and Parson's experimental data can be explained is uncertain, but one suggestion might be made. Lymphatic flow is probably a measure of the amount of fluid lost from capillaries. In a rabbit's ear, perfusion fluid might pass either through capillaries or arteriovenous anastomoses; the latter, as Grant[7] has shown, are very numerous in the rabbit's ear. Only fluid which actually passed

through the capillaries would contribute to lymph formation. The
pulsating perfusion method is probably the best way to obtain complete
capillary injection. McMaster made no direct observations as to the
route his perfusion substance was taking. Therefore, perfusion with
pulsating pressure might have caused increased lymphatic flow simply
because the capillaries were better perfused.

SUMMARY

Cutaneous lymphatic flow may be increased or normal in patients
with high blood pressure. When increased, it is frequently, but not in-
variably, associated with increased minute vessel pressure.

REFERENCES

1. Landis, E. M.: Micro-Injection Studies of Capillary Permeability. ii. The
   Relation Between Capillary Pressure and the Rate at Which Fluid Passes
   Through the Walls of Single Capillaries, Am. J. Physiol. 82: 217, 1927.
2. Landis, E. M.: Capillary Pressure and Capillary Permeability, Physiol. Rev.
   14: 404, 1934.
3. McMaster, P. D.: Changes in Cutaneous Lymphatics of Human Beings and in
   Lymph Flow Under Normal and Pathologic Conditions, J. Exper. Med. 65:
   347, 1937.
4. McMaster, P. D.: Lymphatics and Lymph Flow in Edematous Skin of Human
   Beings With Cardiac and Renal Disease, J. Exper. Med. 65: 373, 1937.
5. Parsons, R. J., and McMaster, P. D.: Effect of Pulse Upon Formation and Flow
   of Lymph, J. Exper. Med. 68: 353, 1938.
6. McMaster, P. D., and Parsons, R. J.: Effect of Pulse on Spread of Substances
   Through Tissues, J. Exper. Med. 68: 377, 1938.
7. Grant, R. T.: Observations on Direct Communication Between Arteries and
   Veins in the Rabbit's Ear, Heart 15: 281, 1930.

STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

IV. BLOOD VOLUME

J. Q. GRIFFITH, JR.,* M.D., R. B. RUTHERFORD, M.D., E. ROBERTS, M.D.,
AND M. A. LINDAUER, M.D.

PHILADELPHIA, PA.

INCREASE in blood volume has not been generally accepted as a possible factor in the development of hypertension. Rowntree, et al.,[1] and Levin[2] found that there was a greater spread of values for blood volume in hypertensive subjects without obvious renal disease than in normal persons, but the averages were about the same. Levin[2] reported a number of cases of hypertension, with associated renal disease, in some of which the blood volume was elevated, and Rowntree, et al.,[1] found that there is a tendency toward high values in nephrosis. If hypertension is indeed an entity, the study of a small series of cases would justify a conclusion. If hypertension is not an entity, it would be necessary to measure the blood volume in every form of hypertension before making a generalization. The results of animal experimentation show that in induced hypertension the blood volume is not necessarily normal. The view will be emphasized that there is a type of hypertension which is associated with, and perhaps secondary to, increased blood volume.

Blood volume has been reported as normal in (1) Goldblatt's form of renal hypertension[3]; (2) the vascular hypertension that follows the intracisternal injection of colloidal kaolin[4]; and (3) the hypertension that follows the repeated injection of pitressin in antidiuretic doses (as described in Part V).

Blood volume has been found to be increased in (1) the hypertension that follows the extravascular injection of 15 c.c. of water or physiologic saline per 100 Gm. of body weight[5]; (2) the hypertension that follows the administration by stomach tube of 5 c.c. of water per 100 Gm. of body weight, together with an antidiuretic dose of pitressin given intraperitoneally (as described in Part V); and (3) the Chanutin-Ferris type of renal hypertension.[6]

Blood volume has been found to be low in (1) the hypertension that follows the intravenous injection of adrenalin[7]; (2) the hypertension that soon follows the intraperitoneal injection of pitressin in pressor doses (as described in Part V); and (3) the hypertension that appears a week or more after the intraperitoneal injection of ergotamine tartrate.[8] In addition, the blood volume was found, by Harris and Gibson,[9] to be

low in glomerulonephritis, frequently when there was an associated hypertension, and low values also occur in eclampsia with hypertension.[10]

It seemed that the subject might be worth reinvestigating. The choice of method required consideration. There are three general types of dye methods: (1) the original method of Rowntree, et al.,[1] later used extensively by Levin[2]; (2) the method of Sunderman and Austin[11]; and (3) the method of Gibson and Evans.[12]

METHOD

The method chosen was that of Sunderman and Austin.[11]* At first, the Congo red recommended by these authors was used; later, Evans blue (T1824), as recommended by Gibson and Evans,[12] was employed.

Results have been variously reported in terms of body weight (Rowntree, et al.,[1] Levin,[2] Sunderman and Austin[11]), surface area (Gibson and Evans[12]), and height (Harris and Gibson[9]). Gibson uses height alone when edema or some other factor might be thought to influence body weight. It was finally decided to express the results in terms of body weight, although surface area might be preferable if the subjects were of definitely abnormal proportions.

METHOD

The subjects were taken from the wards and dispensaries of the hospital of the University of Pennsylvania. As a rule, patients with hypertension were chosen, although an occasional patient with normal blood pressure was included as a control. A large series of normal controls was considered unnecessary, in view of the standards for serum volume previously set up by Sunderman and Austin.[11] Although patients with hypertension were chosen somewhat indiscriminately, an attempt was made to include patients with relatively severe hypertension, especially those with papilledema, and to exclude patients with congestive heart failure.

The patient was brought to the laboratory at 9 A.M., without breakfast. Early in the investigation the basic technique of Sunderman and Austin[11] was followed throughout. The vein used for the injection was never utilized for the collection of samples, and usually a vein of the opposite arm was chosen. When the dye was changed to Evans blue, it was found necessary to give only 20 mg., regardless of the patient's weight. This was dissolved in 7 c.c. of distilled water, and, as a rule, samples were taken at the same intervals as when Congo red was used. If it became necessary to reduce the number of venipunctures, one or two samples only were taken. In every case standards were prepared by adding dye from the same ampoule as that used for the injection to appropriate dilutions of the patient's own dye-free serum (i.e., serum obtained before the injection of dye). Hematocrit determinations were made in duplicate, and blood volume was calculated from the serum volume and average hematocrit reading.

Estimations by the Congo red method were made with a Vim Sheftel (visual) colorimeter; the Evans blue values were read in a Klett-Summerson photoelectric colorimeter. The measurements appeared to be comparable in every way, but the blood level of Evans blue tends to remain more constant than that of Congo red, and, therefore, repeated samplings at thirty-minute intervals are less important

with the former. As a rule, it made a difference of less than 1 c.c. per kilogram of body weight whether the calculations were made from the thirty-minute, 60-minute, or 90-minute sample, or the average of all three. The differences were not sufficiently great nor uniform to justify extrapolating to 0 time, as recommended by Sunderman and Austin[11] for Congo red.

Some, but not all, of the patients whose blood volume was estimated also had measurements of minute vessel pressure and cutaneous lymphatic flow. These were not made in many cases because the study of blood volume was commenced before the other investigations were begun. Moreover, it was not practicable to make blood volume measurements on all patients on whom the other observations had been made.
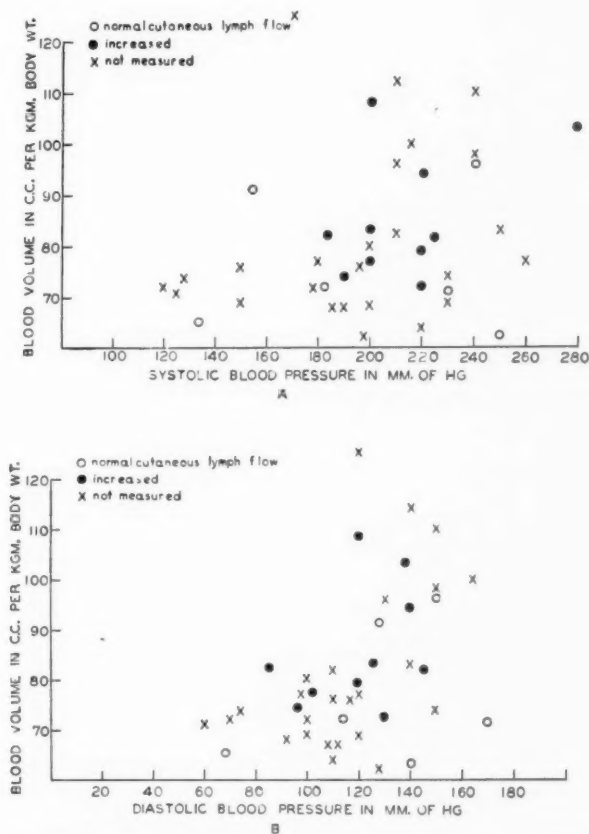
Fig. 1.—A, Chart showing relation between blood volume, systolic blood pressure, and cutaneous lymph flow. For details, see text. B, Chart showing relation between blood volume, diastolic blood pressure, and cutaneous lymph flow. For details, see text.

RESULTS

The blood volume varied from 62 to 120 c.c. per kilogram of body weight. Values of more than 100 c.c. must be considered somewhat less accurate because a secondary dilution of standards was required. It is probable that 78 c.c. per kg. of body weight is the upper limit of normal with this method. If this limit be accepted, it will be seen (Figs.

1*A* and *B*) that eighteen of forty-one estimations showed some increase
in blood volume. There was no consistent relation with the degree of
hypertension, at least none with systolic pressure (Fig. 1*A*), but it will
be seen that high blood volume was usually associated with a diastolic
pressure of more than 120 (Fig. 1*B*). However, with high diastolic
pressures, as well as with high systolic pressures, many persons had
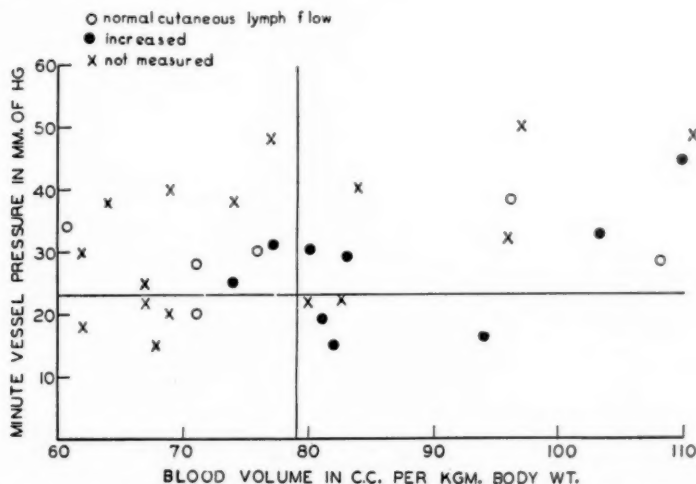normal blood volume.

Fig. 2.—Chart showing relation between blood volume, minute vessel pressure, and
cutaneous lymph flow. For details, see text.

Measurements of cutaneous lymphatic flow were too few to be con-
clusive, but no consistent correlation of blood volume with lymphatic
flow was evident. However, in Fig. 2, in which blood volume is shown
in relation to minute vessel pressure and cutaneous lymphatic flow, there
is a suggestion of correlation between high blood volume and increased
cutaneous lymphatic flow, and, in the three subjects with increased blood
volume and normal minute vessel pressure whose cutaneous lymphatic
flow was measured, it was found to be increased.

DISCUSSION

*A. Schematic Presentation of the Relations Which We Believe May
Be Properly Postulated Between Minute Vessel Pressure, Cutaneous
Lymphatic Flow, and Blood Volume.*—The relations between blood vol-
ume, minute vessel pressure, and cutaneous lymphatic flow are ob-
viously complex. The following hypothetical schema should be read with
reference to Fig. 3.

General considerations.—1. Assume that the introduction of water
into the blood stream, either from the gastrointestinal tract (*B*) or
directly by injection, tends to result in (a) increased urine formation
and excretion (*K*), (b) increased blood volume (*C* + *M*), and (c) in-

creased cutaneous lymphatic flow (L). If the amount introduced is
not excessive, assume that the only measurable effect will be increased
urine elimination (K).

2. Excretion of water through the kidney may be interfered with by
(a) a deficiency in the number of functioning nephrons (H), or (b)
increased resorption of water through the tubules (J); the latter may
perhaps be caused by posterior pituitary hormone. A similar effect may
be produced by a deficiency in the blood supply to a normal number of
nephrons (reduction in E), but under such circumstances we suspect
that a pressor substance from ischemic renal tissue may be a complicat-
ing factor. Under conditions (a) and (b), assume that blood volume
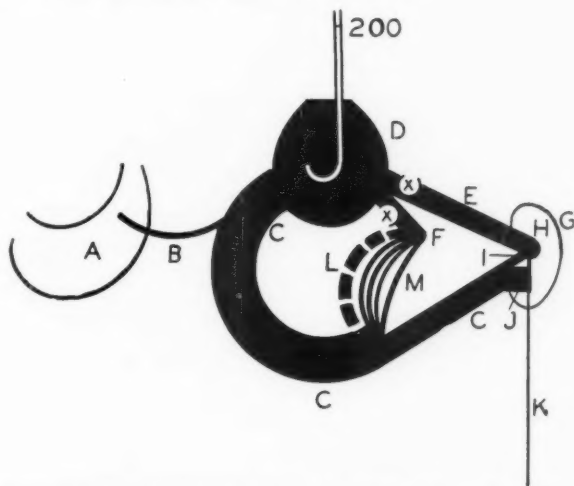and cutaneous lymphatic flow tend to increase.

Fig. 3.—Diagram of organs and channels concerned with transfer of water. A,
the stomach, representing the gastrointestinal tract ; B, water in vessels concerned with
absorption from gastrointestinal tract. Water is shown as solidly filled in black
areas, as follows: C, in the venous system ; D, in the heart ; E and F, in the arterial
system ; H, in the glomerulus ; I, in the efferent vessels of the glomerulus ; J, in the
efferent vessels of the tubules, indicating tubular resorption ; K, in the urine ; L, in
the tissue lymph ; M, in the capillaries. G indicates the kidney. Blood pressure
(unlettered) is represented by a manometer extending from the heart. It is shown
as being elevated, although this is not necessarily the case. For details, see text.

3. Assume that a compensating arteriolar constriction (x) may oc-
cur in any condition in which cutaneous lymphatic flow tends to increase,
and that this may actually prevent such an increase. It may also tend
to prevent an increase in blood volume. However, such compensating
mechanisms might fail, and arteriolar constriction might be associated
with high blood volume and increased cutaneous lymphatic flow. This
type of ''compensatory'' arteriolar constriction should be differentiated
from ''primary'' arteriolar constriction, in which there is no inter-
ference with fluid transfer and the arteriolar constriction is the primary
cause of the hypertension.

4. Arteriolar constriction tends to be associated with hypertension,
and vice versa.

TABLE I

SECONDARY OR ASSOCIATED	PRIMARY VARIATION											
	B			x	+	++	J		+++	H − OR E − OR H AND E −		
	+	++	0									
B.V. (C+M)	++	++	0	0	0	+	+	0	+	+	+	0	0
B.P.	0	+	+	+	+	0	0	+	+	+	+	+	+
M.V.P.	0	+	+	+	+	0	+	0	0	+	+	+	+
x	+	+	+	+	0	0	+	+	+	+	+	+	+
H	+	+	0	+	0	0	+	+	+	−	−	−	−
I	+	+	0	+	0	0	+	+	+	−	−	−	−
J	++	+	0	+	0	0	+	+	+	0	0	0	0
K	++	+	0	0	0	+	0	0	+	+	+	1	+
C.L.F. (L)	+	0	+	0	0	−	−	0	0	+	+	0	+

++, greatly increased; +, increased; 0, no change; −, decreased; B.P., blood pressure; M.V.P., minute vessel pressure; C.L.F., cutaneous lymphatic flow. For significance of other letters see Fig. 3.

5. When there is no interruption of flow, capillary pressure can probably never rise very high because any elevation would simply result in increased fluid loss into the tissues, and this would lower capillary pressure. With obstruction on the venous side, however, capillary pressure may be high because early loss of fluid may result in a concentration of plasma protein sufficient to prevent further loss. In general, however, increased cutaneous lymphatic flow (representing fluid lost from the capillaries) would tend to lower minute vessel pressure.

6. Arteriolar constriction interposes resistance to blood flow, so that, as contrasted with the "normal" state, pressure will be high proximal to it and low distal to it. If the zone of constriction includes the precapillary arteriole, minute vessel pressure, as measured by the method described in Part II, will be high. However, if the zone of constriction ends proximal to the precapillary arteriole, minute vessel pressure will not be increased.

Some of the various combinations that may result are listed in the successive columns of Table I, which should be read with reference to Fig. 3. Although the changes of water content in various parts of the renal mechanism are conjectural, it is nevertheless suspected that the combinations suggested in the table have actually been encountered clinically.

B. Types of Elevated Blood Volume.—Increases in blood volume may be divided into two major types, metabolic and vascular. By a metabolic increase in blood volume is meant the increase that follows primary increase of water in the blood. This may result from addition of fluid in an excessive amount, or from interference with the normal processes by which it is eliminated. For example, Austin and McGuinness[13] reported the case of a patient who was given a large dose of acacia intravenously, and subsequently developed a marked, but transient, hypertension. In this case the presence of the acacia prevented the normal elimination of fluid. However, the same phenomena should occur, but to a lesser extent, following the intravenous injection of excessive amounts of any solution. Failure of elimination is, in all probability, the cause of the high blood volume which is associated with the hypertension in rats made hypertensive by the Chanutin-Ferris type of kidney operation.[6] This metabolic type of increased blood volume is discussed in Section A, and its possible relations have been indicated.

By a vascular increase in blood volume we mean the increase which must occur whenever, for any reason, there is a decrease in vascular tone. It is postulated that the increase in blood volume is of this vascular type in the following: (1) in experimental hyperthyroidism in rats, as reported by Griffith and Comroe[14]; (2) in clinical hyperthyroidism, as reported by Chang[15] and others; (3) after bilateral lumbar sympathectomy, as reported by Griffith, Comroe, and Zinn[8]; and (4) during the

recovery phase following the general vasoconstriction produced by ergotamine, as reported by Griffith, Comroe, and Zinn.[8]

We assume that, with increased blood volume of the vascular type, hypertension does not occur and minute vessel pressure is not elevated. Cutaneous lymphatic flow would usually be normal, but some increase might be expected if the plasma protein were sufficiently diluted to lower the colloidal osmotic pressure.

The patients whose increased blood volumes are shown in Figs. 1A and B and two others probably had the metabolic variety. However, it is sometimes impossible to be sure which type is present in a particular case. For example, a boy, 14 years old, had recovered from an attack of acute glomerulonephritis. During the attack his blood pressure was 190/110, but at the time his blood volume was measured it had fallen to 140/90. His blood volume was 92 c.c. per kilogram of body weight (not charted). Other studies as described in Parts I, II, and III were not made, as this was one of the earliest cases in the series. The elevated blood volume may have been of the metabolic type and have arisen from a condition that had been present during the acute attack; or, it may have been caused by a generalized vascular relaxation which occurred in the recovery phase, after a period of intense vasoconstriction (vascular type).

Another man was studied upon two occasions. At first, when he was in fairly good condition, his blood pressure and minute vessel pressure were high and his blood volume was normal. Unfortunately, the technique for measuring cutaneous lymphatic flow was not then available. Studies were repeated some six months later, a few weeks before his death. At that time his blood pressure had fallen somewhat, but was still high; his minute vessel pressure was normal; his blood volume was high; and his cutaneous lymphatic flow was greatly increased. It is suggested that a terminal diminution in arteriolar tone permitted the development of a vascular type of increase in blood volume.

C. Relation Between Blood Volume and Minute Vessels.—Observation of cutaneous vessels suggests that there are certain interrelations between blood volume and minute vessels. An arteriole and its cluster of capillaries might be regarded as the smallest vascular unit. Under normal circumstances it is probable that, throughout much of the body, every arteriole is open part of the time and closed part of the time. Under certain conditions the relative duration of these phases may change. For example, in polycythemia vera, an increase in blood volume must be accommodated. Therefore, the arterioles may be open more of the time, or even all of the time. The authors have noted that, in polycythemia vera, all of the cutaneous capillaries in the forearm are open, and that no more are visible after the injection of histamine. This would also explain the observations of Roberts and Griffith[16] in cases of hyperthyroidism.

Another way in which more blood could be accommodated in a given vascular bed would be dilatation of vessels that are ordinarily open. Undoubtedly both of these vascular changes occur, although their relative importance is uncertain. However, it may be accepted as probable that arterioles which, by dilating or constricting, can empty or fill peripheral vascular beds (capillaries) exert an effect on blood volume far out of proportion to that produced by changes in their size. This indicates the peculiarly strategic position of the arterioles in the regulation of blood pressure and blood volume. It is frequently implied that the maximal point of resistance on the arterial side of the capillaries lies in the arterioles, and, by comparing the relative size of the arterioles and larger arteries, this implication appears to be justified. However, because of the normal branching of the arterial tree, it appears that the summated cross section of vessels of any caliber normally exceeds the sum of the cross sections of vessels between them and the heart. It is the tremendous expansion of the vascular bed in the capillaries that accounts for the sharp drop in pressure between the arterioles and the capillaries. The importance of the arteriole lies in its ability to shut off this capillary vascular bed. However, under pathologic conditions, it is possible that the arterioles may assume a barrier role, with a total cross-sectional area less than that of proximal, small arteries.

High blood volume is infrequently associated with high blood pressure, certainly less often than might be suggested by the observations here presented. This was the result of our method of selecting cases, and will be referred to again in Parts V and VII.

SUMMARY

Blood volume is usually normal in patients with high blood pressure, but in certain instances it is increased. An increase of blood volume in cases of hypertension is always associated with increased minute vessel pressure, or increased cutaneous lymphatic flow, or both. In an attempt to account for this, various theories are discussed.

REFERENCES

1. Rowntree, L. G., Brown, G. E., and Roth, G. M.: The Volume of Blood and Plasma, Philadelphia, 1929, W. B. Saunders Co.
2. Levin, E.: El volumen de la sangre circulante, Rosario. Establ. Graf. Pomponio, 1938.
3. Freeman, N. E., and Page, I. H.: Hypertension Produced by Constriction of Renal Artery in Sympathectomized Dogs, AM. HEART J. 14: 405, 1937.
4. Griffith, J. Q., Jr., and Roberts, E.: Further Studies in the Mechanism of Vascular Hypertension Following the Intracisternal Injection of Kaolin in the Rat, Am. J. Physiol. 124: 86, 1938.
5. Griffith, J. Q., Jr.: Studies in Blood Volume and Blood Pressure Following the Extravascular Administration of Fluid in Rats, Am. J. Physiol. 122: 140, 1938.
6. Griffith, J. Q., Jr., and Ingle, D. J.: Studies of Blood Volume in Experimental Hypertension Following Subtotal Nephrectomy. Effect of Posterior Pituitary Lobectomy, Proc. Soc. Exper. Biol. & Med. 44: 538, 1940.

7. Freeman, N. E.: Decrease in Blood Volume After Prolonged Hyperactivity of the Sympathetic Nervous System, Am. J. Physiol. 103: 185, 1933.
8. Griffith, J. Q., Jr., Comroe, B. I., and Zinn, C. J.: Studies of Blood Volume in Ergotamine Tartrate Poisoning in Rats, Proc. Soc. Exper. Biol. & Med. 40: 177, 1939.
9. Harris, A. W., and Gibson, J. G., 2nd: Clinical Studies of Blood Volume. VII. Changes in Blood Volume in Bright's Disease With or Without Edema, Renal Insufficiency, or Congestive Failure, and in Hypertension, J. Clin. Investigation 18: 527, 1939.
10. Dieckmann, W. J.: Blood Volume and Plasma Volume Changes in Eclampsia, Am. J. Obst. & Gynec. 32: 927, 1936.
11. Sunderman, F. W., and Austin, J. H.: The Measurement of Serum Volume, Am. J. Physiol. 117: 474, 1936.
12. Gibson, J. G., 2nd, and Evans, Wm. A., Jr.: Clinical Studies of the Blood Volume. I. Clinical Application of a Method Employing the Azo Dye ''Evans Blue'' and the Spectrophotometer, J. Clin. Investigation 16: 301, 1937.
13. Austin, J. H., and McGuinness, A. C.: A Precaution Concerning the Treatment of Edema by Intravenous Administration of Acacia, Tr. A. Am. Physicians 48: 276, 1933.
14. Griffith, J. Q., Jr., and Comroe, B. I.: Reduced Tolerance to Ergotamine Tartrate in Hyperthyroidism, J. Pharmacol. & Exper. Therap. 69: 34, 1940.
15. Chang, H.: Blood Volume in Hyperthyroidism, J. Clin. Investigation 10: 475, 1931.
16. Roberts, E., and Griffith, J. Q., Jr.: A Quantitative Study of Cutaneous Capillaries in Hyperthyroidism, Am. Heart J. 14: 598, 1937.

STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

V. Types of Hypertension Associated With the Presence of Posterior Pituitary Substance

J. Q. Griffith, Jr.,* M.D., H. O'Brien Corbit, A.M.,
R. B. Rutherford, M.D., and M. A. Lindauer, M.D.
Philadelphia, Pa.

EXPERIMENTAL AND CLINICAL STUDIES

CUSHING[1] focused attention upon the role of the pituitary in hypertension when he described "the posterior lobe basophilia of eclampsia, of essential hypertension, and of the atheroscleroses and nephropathies of the aged." Further study of the problem has followed four general channels:

1. The effect of the administration, usually by injection, of extracts derived from the pituitary glands of animals to other animals or man.

2. The effect on animals of the vascular changes which result from the administration of such substances (see, for example, Scheps[2]).

3. Attempts to identify substances, presumably derived from the pituitary, in the blood, urine, or cerebrospinal fluid of man or animals. This has led to the development of many biologic tests and to the collection of many more or less discordant data (see, for example, Anselmino and Hoffman[3]; Teel and Reid[4]; Byrom and Wilson[5]; Melville[6]; Jones[7]; Noble, Rinderknecht, and Williams[8]). Attempts have been made to increase the production of pituitary hormone by some physiologic stimulus. For example, Gilman and Goodman[9] deprived rats of water in order to stimulate the secretion of antidiuretic hormone.

4. Attempts to modify the effects of pituitary hormones by the simultaneous administration of extracts of other glands (see, for example, Shapiro[10]), or by deliberately stimulating or depressing other glands, such as the ovary.

In spite of the mass of facts that has been collected, it is difficult to make a diagnosis of a "pituitary" form of hypertension, and, indeed, there is no uniform agreement that such a type actually exists. The difficulties involved in the clinical use of the information available are as follows: (1) Standards based upon histologic study of the pituitary are seldom of any use to the patient who supplied the pituitary. (2) Study of the effects of pituitary extracts upon the experimental animal, especially as concerns hypertension, has been handicapped by failure to recognize and classify various types of hypertension. (3)

Biologic tests which rely upon elaborate extractions of urine or serum may be falsely positive or negative as a result of changes in the test material which occurred during the extraction. (4) There is no clinical method of confirming biologic tests. The nearest approach to such confirmation occurred in the case reported by Jones[7] and Noble, Rinderknecht, and Williams,[8] in which the biologic tests became less positive as the patient improved. (5) There is the possibility that disturbance of the endocrine balance in either the patient or the test animal may lead to erroneous results.

Preparations derived from the posterior lobe of the pituitary contain a pressor hormone and an antidiuretic hormone. Therefore, one might expect a difference in the hypertensive response of an animal to a pituitary preparation, depending upon the state of hydration of the animal.

The plan, therefore, was (1) to study hypertension produced by pituitary substances in the experimental animal, under varied circumstances, and to try to establish certain objective standards, such as those described in Parts I through IV, which might be used in the clinical recognition of pituitary hypertension; (2) to develop a biologic test on blood instead of urine, and to minimize the effect of artifacts by avoiding extraction; and (3) to follow the effect, in suitable cases, of pituitary irradiation.

A. EXPERIMENTAL STUDIES

1. *Effect of Large Doses of Pitressin* on Blood Pressure (Pressor Effect) and Blood Volume.*—In many preliminary experiments it had been found that rats which were injected with 0.1 pressor unit, or more, per 100 Gm. of body weight developed vascular hypertension, as measured by the indirect method of Griffith.[11] The blood volume of ten normal rats was measured by the dye method of Griffith and Campbell.[12] Several days later, under nembutal anesthesia, each animal was given 5 pressor units of pitressin intraperitoneally. This was considered a large dose, and had repeatedly produced a marked hypertension (200 mm. of mercury, or more) which lasted several hours. Thirty minutes later blood volume was again measured. The results are tabulated in Table I. Normal blood volume varies between 4.0 and 5.3 c.c. per 100 Gm. of body weight. It will be seen that in every case the blood volume had decreased, in nine instances to pathologic levels.

TABLE I

RAT NO.	1	2	3	4	5	6	7	8	9	10
Weight (Gm.)	158	217	170	180	180	170	152	185	180	190
B.V. before P.	5.1	4.9	4.7	4.8	5.3	4.5	4.3	5.6	4.8	4.8
B.V. after P.	3.8	4.3	3.8	2.4*	2.4*	2.6	2.8*	2.3*	2.4*	2.2*

B.V., blood volume; P., pitressin. Blood volume figures are expressed in cubic centimeters per 100 Gm. of body weight.

*Actual blood volume was somewhat less, but standards were so established that, in the colorimeter, smaller values could not be read accurately.

*Parke, Davis and Co. Each cubic centimeter contained 20 pressor units.

2. *Effect of Small Doses of Pitressin (Antidiuretic Effect).*—The procedure was approximately as follows: (1) The effect of water: (a) A preliminary blood pressure measurement was made under ether anesthesia. The fact that the pressure was normal was thus established. (b) One or two days later, without anesthesia, the rat was given 5 c.c. of water per 100 Gm. of body weight by stomach tube. It was then placed in a metabolic cage and urine was collected for 1½ hours. Then a blood pressure measurement was made under ether anesthesia, as before. (2) The effect of pitressin: (a) About a week later a blood pressure measurement was made to be sure that the pressure was normal. (b) A day or two later each rat was given, intraperitoneally, 0.12 c.c. per 100 Gm. of body weight of a solution of pitressin diluted 1:150 with distilled water. (This dosage was suggested by the work of Burn,[13] and corresponds to slightly over 5 milli-units of antidiuretic hormone. It was chosen because in preliminary work with larger doses it was thought that some animals showed direct pressor effects. Walker[14] states that he was unable "to detect the antidiuretic effect of much less than 4 mU per 100 grams" in rats which received 5 c.c. of water per 100 Gm. by stomach tube.) The urine collection and blood pressure measurement were made after the same interval as before. (3) The effect of water and pitressin: (a) After a rest period of a week, another blood pressure measurement was made to be sure that the pressure was normal. (b) A day or two later each rat was given, without anesthesia, 5 c.c. of water per 100 Gm. of body weight by stomach tube, and, intraperitoneally, an injection of pitressin in the same dose as before. Again, urine was collected over a period of 1½ hours and the blood pressure measured. In sixteen of these animals blood volume, under ether anesthesia, was measured immediately after taking the blood pressure.

Variations from the above procedure were made in some instances, as follows: (1) In the later steps, new animals were substituted for a few animals which were ill or dying; (2) the interval between experiments was sometimes lengthened to suit convenience; (3) changes were purposely introduced in the order of the three experimental procedures. Both male and female rats were used, but recognizably pregnant females were excluded from the series.

The blood pressure measurements which were obtained after the three procedures are charted in Fig. 1*A*. None of the animals which received water alone in the amounts used in these experiments developed hypertension; the maximal normal blood pressure was taken as 150 mm. of mercury. Of the animals which were given pitressin, one had a blood pressure of 152, but this cannot be considered significantly abnormal. On the other hand, the blood pressure of eleven of thirty-seven animals which received both water and pitressin rose above 150 and ranged to 220.

Fig. 1*B* shows the relation between the water retained (the difference between the water intake and the urine excretion in 1½ hours per 100 Gm. of body weight) and the blood pressure in animals which were given water with, and without, pitressin. There is a direct correlation, although not a very close one. However, the antidiuretic effect of the pitressin is obvious. Animals which received pitressin alone either passed no urine at all, or only a few drops, and therefore the results in that group are not included in this figure.
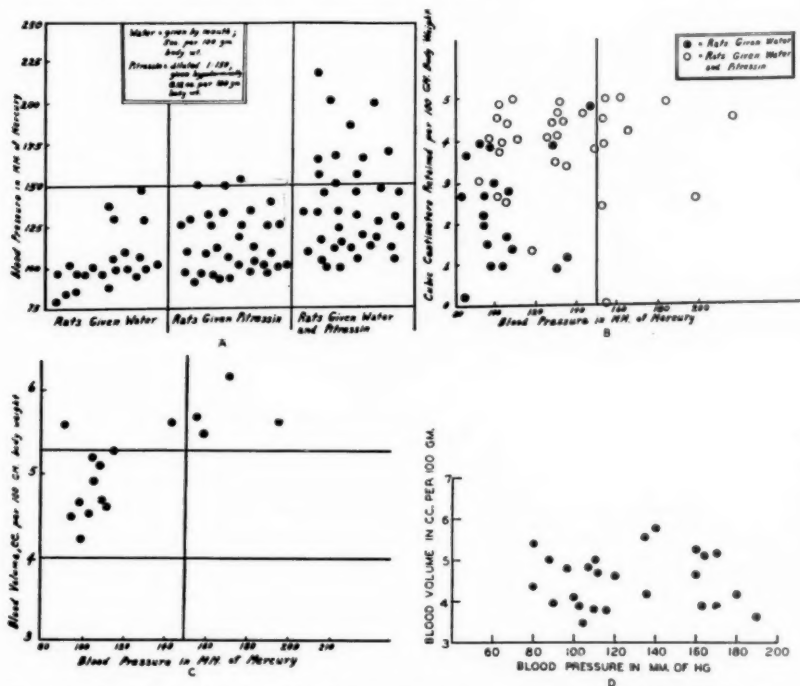

Fig. 1.—*A*, Chart showing blood pressure measurements of animals which were given either water by mouth, or pitressin by injection, or both. For details, see text. *B*, Chart showing the correlation between the antidiuretic effect produced by pitressin and the blood pressure level. *C*, Chart showing the correlation between blood pressure and blood volume in animals which were given both water by mouth and pitressin by injection. *D*, Chart showing the lack of correlation between blood pressure and blood volume in rats which had been made hypertensive by repeated antidiuretic doses of pitressin.

Fig. 1*C* shows the correlation between blood volume and blood pressure in sixteen animals that received both water and pitressin. The correlation is direct. One animal in this series had a definitely elevated blood volume with a low normal blood pressure, but in no case did hypertension occur with a normal blood volume. This series should be compared with one previously reported,[15] in which water or physiologic saline was given to rats, either subcutaneously or intraperitoneally, in the amount of 15 c.c. per 100 Gm. of body weight. A certain number of those animals also developed vascular hypertension which was associated with an increase in blood volume, and occasionally an animal had an increased

blood volume with a normal blood pressure. Likewise, in that series, no animal developed hypertension without a high blood volume. It is probable that the mechanism of production of the hypertension in these two series is identical, i.e., 5 c.c. of water per 100 Gm. of body weight by mouth, together with pitressin, would be about equivalent to 15 c.c. per 100 Gm. of body weight by injection, without pitressin.

3. *Effect of Repeated, Small (Antidiuretic) Doses of Pitressin.*—When the experiments of the type described in the previous section were begun, the same animals were used repeatedly, without specific identification. A rest period was allowed between experiments, but no preliminary blood pressure measurements were made. Finally, it was found that all of the procedures appeared to lead to hypertension, and blood pressure measurements which were made on eleven surviving animals showed that seven of them were continuously hypertensive. Therefore, all of the experiments up to this point (fifty-nine) were discarded, and the more carefully controlled procedure described in the previous section was carried out.

We undertook to ascertain whether the persistence of the hypertension was caused by the repeated administration of pitressin, of water, or of the two combined. Therefore, a group of ten rats was selected, five of which were given water and pitressin, and five only pitressin, on seven occasions over a period of nineteen days. The amounts were the same as those used in Series 2. The blood pressure was measured one day, and eight days, after the final injection. On the first day after the final injection, all of the three surviving animals which were given pitressin alone had hypertension; their blood pressures were 195, 185, and 165, as compared with the preinjection measurements of 60, 120, and 95. Four of the five animals which received water and pitressin survived. Their preinjection blood pressures were 85, 90, 105, and 70. On the first day after the final injection, only one animal had hypertension, with a blood pressure of 162, but by the eighth day three animals had hypertension, with blood pressures of 180, 160, and 168. It appeared, therefore, that the pitressin was the cause of the hypertension. The delay in the appearance of the hypertension in animals which were also given water is explained by the condition of the animals. They were given water at such frequent intervals that they developed diarrhea, and, when their blood pressure was measured on the first day after the final injection, they were quite sick, as compared with the animals which received pitressin alone. The three deaths were caused by the respiratory infection which at that time was sweeping through the rat colony.

Subsequently, twenty-five animals were given the same amount of pitressin at approximately the same intervals, and blood pressure and blood volume were measured one day after the final injection. The results are shown in Fig. 1D. Eight of the twenty-five animals were

definitely hypertensive. The blood volume was normal in all. The dura-
tion of the hypertension was not definitely ascertained. It lasts, as a
rule, eight days or more, and, in one animal, was present (165 mm. of
mercury) at the time of the last measurement, which was four weeks
after the final injection.

The urea nitrogen content of the blood was measured in nine animals,
four of which were hypertensive. It was normal in all cases. The
kidneys of ten animals, four of which had been hypertensive, were
examined histologically by Dr. Herbert Fox and Dr. James Forrester, of
the Pepper Laboratory. No important lesions were found.

DISCUSSION

Thus, in experimental "pituitary" hypertension, the blood volume
may be low (large dose), normal (repeated small doses), or high (small
dose in a hydrated animal). Therefore, one would expect that measure-
ment of blood volume would be of little use in trying to decide whether
a particular patient's hypertension was of the "pituitary" type.

The remaining three objective criteria, as described in Parts I to III,
will be considered separately:

(1) Change in the number of open capillaries. The cutaneous capil-
lary bed in the rat is quite different from that of man. Moreover, in
the rat all studies must be made under anesthesia. The task of estab-
lishing normal standards would be enormous. In consequence, such
standards are not available, and comparisons with conditions in man
are, at present, impossible.

(2) Minute vessel pressure. A technique for measuring minute vessel
pressure in the rat is available, and figures have been reported by
Griffith and Roberts[16] for normal rats and rats made hypertensive by the
intracisternal injection of kaolin. The apparatus described in Part II
can be used, but the technique differs considerably from that employed
in man. The foot of an anesthetized rat is fixed to a mechanical stage
by means of stitches or plasticine, so that the dorsum of the foot is up
and somewhat arched. This is the area selected for the observation. The
compressing chamber is then lowered until skin contact is made, and
the minute vessels are visualized through the microscope. Since these
vessels pass parallel to the skin surface, they usually cannot be ob-
literated by pressure, so that the original Danzer-Hooker end point must
be used, i.e., cessation of flow when the pressure in the chamber is
raised. For reasons given in Part II, what is measured by this method
is pressure in the precapillary arteriole, rather than in the capillary.
Complete reliance is not placed on the method for the following reasons:
(a) When a blood pressure cuff is placed about the thigh of the rat and
the pressure in it is raised somewhat, corresponding increments of minute
vessel pressure do not occur (see Part II, test of accuracy of method

in man).   As a matter of fact, when pressure is applied to the thigh by the cuff, minute vessel pressure usually falls.   This objection may not be valid, however, because of the small size and irritability of the femoral artery of the rat.   If the artery is torn, it usually contracts, and little bleeding occurs.   It contracts markedly after any manipulation, and it is possible that the cuff about the thigh of the rat affects the femoral artery as well as the vein and thus reduces the arterial inflow; in man the cuff affects mainly the venous return.   (b) The rat's foot is thin-skinned, and the bones are very near the surface.   Thus, theoretically, the compressing chamber may obliterate vessels larger than capillaries and arterioles.   This possibility was suggested when it was found that rats which developed high blood pressure following the intra-cisternal injection of kaolin had elevated minute vessel pressure, whereas it had been anticipated that minute vessel pressure would be normal.
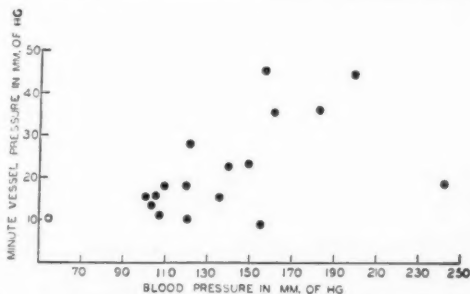

Fig. 2.—Chart showing the correlation between minute vessel pressure and blood pressure in rats which had been injected subcutaneously or intraperitoneally with an amount of water or physiologic saline equivalent to 15 per cent of their body weight.

Therefore, minute vessel pressure was not measured in the present series, but Fig. 2 shows the correlation between minute vessel pressure and arterial pressure in a series of animals which had been made hypertensive by the injection of 15 c.c. of fluid per 100 Gm. of body weight. Although they comprised part of a study made by Griffith, Jeffers, and Lindauer,[17] these particular figures were not reported.   For reasons already given, this form of hypertension is thought to be analogous to that produced by smaller amounts of water and antidiuretic doses of pitressin. It is obvious from Fig. 2 that, under experimental conditions, what was supposed to be minute vessel pressure varied directly with blood pressure.

Therefore, judging from Fig. 2, one might suspect that in certain forms of hypertension which are the result of fluid retention, caused perhaps by pituitary hyperactivity, minute vessel pressure might be elevated.   This is also in accord with the hypotheses advanced in connection with Fig. 3 and Table I of Part IV, where it was suggested that increased blood volume of the "metabolic" type may be associated with

increased minute vessel pressure. Obviously, the increased blood volume which accompanied the hypertension in Series 3 was of the "metabolic" type.

(3) Cutaneous lymphatic flow. It was shown in Part III that rats which had been given water and pitressin in antidiuretic doses sometimes had an increased cutaneous lymphatic flow, but this occurred in animals that did not develop hypertension. This suggested that, in the experimental animal, arteriolar constriction was adequate to prevent excessive loss of fluid from the capillaries. However, in these acute experiments, water and pitressin were given but once, whereas, in diseased states, one would think of the alteration in the processes of water elimination as acting over an indefinitely long period of time. Under the latter circumstances arteriolar constriction might eventually prove inadequate to prevent loss of fluid from the capillaries, and cutaneous lymphatic flow might be increased. Therefore, one might expect such an increase in certain cases of hypertension caused by pituitary hyperfunction.

Most of what has been said concerns the type of pituitary hypertension characterized by an elevated blood volume. However, other forms, or even transitional forms, may well occur, depending upon the amount, or possibly the character, of the circulating posterior lobe hormone. Therefore, to summarize, in hypertension caused by posterior pituitary hyperactivity (1) the blood volume in the acute stage might be high, low, or normal (in the "recovery" phase it might be normal in the presence of persistent hypertension); (2) minute vessel pressure might be increased; (3) cutaneous lymphatic flow might be normal or increased; (4) papilledema, which, as will be shown in Part VII, occurs frequently in the presence of a metabolic increase in blood volume, might be present; and (5) following a period of pituitary hyperactivity, hypertension might persist even after such activity had subsided. Perhaps during the acute phase certain arteriolar changes occur which require time to regress or may even become permanent. The blood volume should be normal in such cases, and, as the rats during the recovery phase after small doses of pitressin seemed quite well, the clinical condition of the patients should be good. All tests for an excess of posterior lobe substance should be negative. The diagnosis could be made only if the patient had been observed in the preceding period, during which there had been evidence of pituitary hyperactivity.

B. CLINICAL STUDIES

The Biologic Test.—The test was based on the method of Burn[13] for assaying the antidiuretic content of pituitary substance, and, in the last analysis, is the same as the procedure employed in Series 2 of the animal experiments, except that 1 c.c. of serum was injected instead of the pitressin.

METHOD

The patient was not prepared in any way. About 10 c.c. of blood was drawn by venipuncture and permitted to clot. The serum was separated, by centrifuging when necessary. As in Series 2 of the animal experiments, rats were given 5 c.c. of water per 100 Gm. of body weight by stomach tube. Passing the stomach tube always caused the animals to empty their bladders. One cubic centimeter of the patient's serum was then injected intraperitoneally, and the animal was placed in a metabolic cage. The volume of urine which was passed at the end of ninety minutes was then measured; complete emptying of the bladder was assured by holding the animal and giving it a few whiffs of ether. The amount of urine voided was subtracted from the amount of water given, and the difference was expressed as cubic centimeters retained per 100 Gm. of body weight. From Fig. 1B it is apparent that normal animals, with rare exceptions, when given water alone, retain less than 4 c.c. per 100 Gm. of body weight, usually considerably less. This fact, together with clinical experience, suggests that retention of 4 c.c., or more, per 100 Gm. of body weight is abnormal. In a few cases the blood pressure was measured under ether anesthesia at the end of the ninety-minute period. Sometimes the degree of dilution of plasma protein was measured by ascertaining the refractometric indices before, and at the end of, the ninety-minute period.

In many instances a simple melanophore expanding test was done simultaneously on the same serum. The technique, based upon suggestions made in Van Dyke's monograph,[18] was as follows: Frogs which had been matched for color were placed in individual containers in "artificial daylight." After a period of thirty minutes or more, when the colors appeared to be constant, the one that was slightly the lighter was injected under the skin of the back with 1 c.c. of patient's serum. The frogs were observed for twenty minutes, and, if the injected frog darkened definitely, as compared with the other, the test was considered positive. This is thought to be a test for hormone from the pars intermedia.

On most of the patients, capillary counts and measurements of minute vessel pressure and cutaneous lymphatic flow were also made; in some cases, blood volume was estimated.

TABLE II

PATIENTS WITH HYPERTENSION

	ANTIDIURETIC TEST	
	+	−
Minute vessel pressure normal	2	11
high	21	16
Cutaneous lymphatic flow normal	10	15
increased	12	13
Both minute vessel pressure and cutaneous lymphatic flow normal	0	8
Blood volume normal	2	4
increased	4	5
Papilledema present	8	5
absent	12	18
Melanophore expanding test negative	12	17
positive	3	1*
Sex—male	8	11
female	18	18
Age—range	25-57	17-60
average	40	38
Total	26	29

*Patient with a pituitary tumor.

RESULTS

Fig. 3 shows the result of the antidiuretic tests when the sera of normal persons were used. In some cases one rat of the three which were given the subject's serum showed an antidiuretic effect, but never more than one. Figs. 4A and B show the result of similar tests on persons with hypertension. Fig. 4A includes the patients who behaved like normal subjects, and Fig. 4B comprises those whose sera gave an antidiuretic

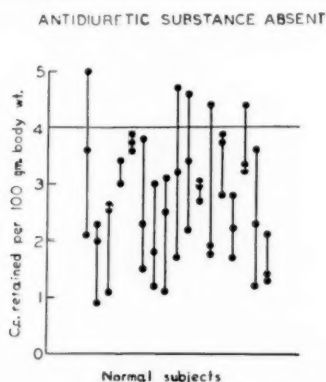ANTIDIURETIC SUBSTANCE ABSENT

Fig. 3.—Chart showing the amount of water retained over a ninety-minute period, in terms of cubic centimeters per 100 Gm. of body weight. Each animal was given 5 c.c. of water per 100 Gm. of body weight by stomach tube, and 1 c.c. of the serum of a normal person intraperitoneally at the beginning of the test. The three rats used for each subject are indicated by a vertical line joining the dots.

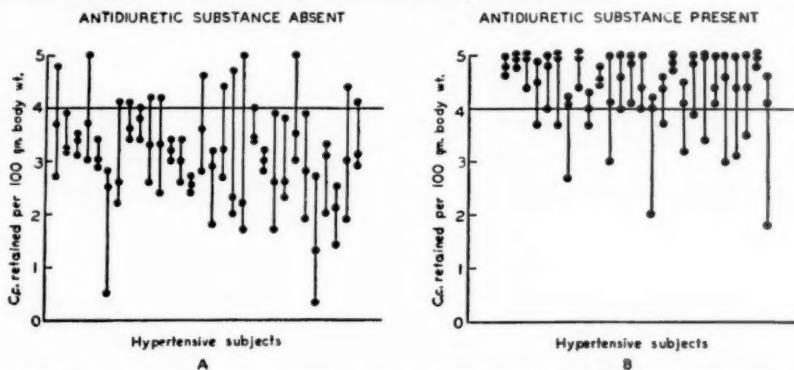ANTIDIURETIC SUBSTANCE ABSENT   ANTIDIURETIC SUBSTANCE PRESENT

Fig. 4.—A, Same as Fig. 3, except that the sera were obtained from patients with high blood pressure and did not contain an antidiuretic substance for rats. B, Same as Fig. 4A, except that the blood of this group of hypertensive patients did contain an antidiuretic substance for rats.

effect in two or three of the three rats. The characteristic features of the two groups are compared in Table II, but the comparison is not entirely a fair one. It became obvious fairly early in the study that the typical patient with increased posterior pituitary lobe activity (assuming that this is demonstrated by the test) and hypertension had an increased minute vessel pressure and a better than 50 per cent chance of having an increased cutaneous lymphatic flow. Therefore, patients were later selected for study on the basis of these criteria, with the result that these phenomena were observed in many of the patients who had

negative tests. A positive test for melanophore expanding substance seldom occurs, but, when it does, it is perhaps confirmatory. The differences in total figures on certain tests are the result of including a few negroes.

DISCUSSION

The presence of an antidiuretic substance in the serum does not necessarily indicate increased activity of the posterior lobe of the pituitary. Walker[14] found such substances in the urine of animals, both under conditions of hydration and dehydration, and after hypophysectomy. However, such a substance could originate in the posterior lobe of the pituitary, and it affects diuresis in the same way as pitressin. The stimulus to posterior lobe secretion in dehydrated animals is not necessarily comparable quantitatively with that which may occur in patients under pathologic conditions. The best evidence to suggest that such an antidiuretic substance is of pituitary origin is the fact that it disappeared after adequate pituitary irradiation in fifteen cases. Although it usually tends to recur, in one case in which there was no hypertension, reported by Edeiken and Griffith,[19] there has been no recurrence over a nine-month period. In one case of hypertension the antidiuretic substance disappeared for six months. During the first two months of this period the systolic blood pressure fell from 200 to 130 and remained low for four months. However, the antidiuretic substance returned, and two weeks later the blood pressure had risen to 180, and a week later to 190. After further irradiation the substance disappeared, and the blood pressure returned to 128. It is too early to evaluate the results in this case. In general, however, the amount of reduction in pressure is likely to be disappointing. Headaches may be relieved at first. Papilledema has disappeared in two cases. The study of the treatment of such patients by irradiation will be continued, and reported with Dr. Pendergrass and Dr. Hodes. At the present time it is mentioned primarily to lend support to the suggestion that the antidiuretic substance in the serum is of pituitary origin.

Positive tests for the antidiuretic substance have been obtained in persons without high blood pressure, and in certain cases in which the existence of true pituitary disease appeared to be unlikely. These include patients with malignant tumors, pregnant women, and one patient with recurring duodenal ulcer. Further study of such cases is in order, but their occurrence suggests that complete acceptance of the test as an indication of posterior pituitary disease must be deferred. However, in those cases in which the test can be changed from positive to negative by pituitary irradiation, the evidence is considerably stronger. Such a test of irradiation has not been employed except in patients with hypertension and women with symptoms presumably caused by fluid retention during menstruation.

Hypertension and plasma protein dilution occur in certain rats that have been injected in the usual manner with serum containing antidiuretic substance. To measure these changes greatly complicates the test, and it is not certain that thereby one adds to the percentage of true positives. Whether these measurements can be safely omitted is a question that the future must decide. The evidence collected to date suggests that they can be omitted.

The fact that the blood pressure does not fall to normal as the antidiuretic substance disappears from the serum may be analogous to the persistence of the hypertension after repeated, small injections of pitressin. When the blood pressure does fall, it does so gradually over a period of about two months.

SUMMARY

Hypertension in rats was produced by giving a single, large dose of pitressin, a single, small dose of pitressin, together with fluid by mouth, and repeated, small doses of pitressin. In the three forms of hypertension, the blood volume was, respectively, low, high, and normal. A biologic test for an antidiuretic substance in the serum of patients is described. This test was positive in certain cases of high blood pressure. Such patients usually have increased minute vessel pressure, about 50 per cent have increased cutaneous lymphatic flow, and some have papilledema. The blood volume may be normal or increased. In such cases the test may become negative after pituitary irradiation, with, usually, some clinical improvement and a variable effect on blood pressure. The test is not specific for posterior pituitary hyperactivity, but, when it is positive in a particular case, it may serve as a measure of the effect of pituitary irradiation. If it subsequently becomes negative, the inference is that the pituitary was at fault.

REFERENCES

1. Cushing, H.: Hyperactivation of the Neurohypophysis as Pathological Basis of Eclampsia and Other Hypertensive States, Am. J. Path. 10: 145, 1934.
2. Scheps, M.: L'influence de la vasopressine sur le systeme cardio-vasculaire chez les animaux, Compt. rend. Soc. de biol. 115: 1367, 1934.
3. Anselmino, K. J., and Hoffman, F.: Die Übereinstimmungen in den klinischen Symptomen der Nephropathie und Eklampsie der Schwangeren mit den Wirkungen des Hypophysenhinterlappenhormons, Arch. f. Gynäk. 147: 597, 1931.
4. Teel, H. M., and Reid, D. E.: Observations Upon Occurrence of Antidiuretic Substance in Urine of Patients With Pre-eclampsia and Eclampsia, Endocrinology 24: 297, 1939.
5. Byrom, F. B., and Wilson, C.: Alleged Pituitary Origin of Eclamptic and Pre-eclamptic "Toxaemias" of Pregnancy, Quart. J. Med. 3: 361, 1934.
6. Melville, K. I.: Antidiuretic Pituitary Substance in Blood With Special Reference to Toxemia of Pregnancy, J. Exper. Med. 65: 415, 1937.
7. Jones, E. I.: New Syndrome Apparently Due to Overactivity of Posterior Pituitary, Lancet 1: 11, 1938.
8. Noble, R. L., Rinderknecht, H., and Williams, P. C.: Clinical Hyperfunction of Posterior Lobe of Pituitary Suggested by Pressor and Antidiuretic Substance Obtained From Urine, Lancet 1: 13, 1938.

9. Gilman, A., and Goodman, L.: Secretory Response of Posterior Pituitary to Need for Water Conservation, J. Physiol. **90**: 113, 1937.
10. Shapiro, B. G.: Control of Urinary Secretion by Anterior Pituitary, Lancet **2**: 1457, 1938.
11. Griffith, J. Q., Jr.: Indirect Method for Determining Blood Pressure in Small Animals, Proc. Soc. Exper. Biol. & Med. **32**: 394, 1934.
12. Griffith, J. Q., Jr., and Campbell, R.: A Method for Determining Blood Volume in Rats, Proc. Soc. Exper. Biol. & Med. **36**: 38, 1937.
13. Burn, J. H.: Estimation of the Antidiuretic Potency of Pituitary (Posterior Lobe) Extract, Quart. J. Pharm. & Pharmacol. **4**: 517, 1931.
14. Walker, A. M.: Experiments Upon the Relation Between the Pituitary Gland and Water Diuresis, Am. J. Physiol. **127**: 519, 1939.
15. Griffith, J. Q., Jr.: Studies in Blood Volume and Blood Pressure Following the Extravascular Administration of Fluid in Rats, Am. J. Physiol. **122**: 140, 1938.
16. Griffith, J. Q., Jr., and Roberts, E.: Further Studies in the Mechanism of Vascular Hypertension Following the Intracisternal Injection of Kaolin in the Rat, Am. J. Physiol. **124**: 86, 1938.
17. Griffith, J. Q., Jr., Jeffers, W. A., and Lindauer, M. A.: Transient Hypertension in Rats Following the Extravascular Administration of Fluid, Am. J. Physiol. **118**: 1, 1937.
18. Van Dyke, H. B.: Physiology and Pharmacology of the Pituitary Body, Chicago, 1939, University of Chicago Press.
19. Edeiken, J., and Griffith, J. Q., Jr.: Cyclical Pulmonary Edema at the Menses Complicating Mitral Stenosis. Relief Following Pituitary Irradiation, J. A. M. A. **115**: 287, 1940.

STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

VI. Treatment With Thiocyanate

J. Q. Griffith, Jr.,* M.D., M. A. Lindauer, M.D., E. Roberts, M.D.,
and R. B. Rutherford, M.D.
Philadelphia, Pa.

SINCE Barker's report,[1] in 1936, potassium thiocyanate has been used in the treatment of hypertension in certain cases from the wards and dispensaries of this hospital and the private practices of the authors. Until April 14, 1940, 168 persons had been so treated. The early results have been reported previously.[2] Only 101 of these 168 patients have been followed long enough and have been under sufficiently close observation to estimate the results of the medication. In fifty-nine cases the treatment has been successful, and in forty-two, unsuccessful. The treatment was regarded as successful when the patient maintained a systolic blood pressure of 170, or lower, a diastolic of 110, or lower, and felt subjectively improved, while the blood content of thiocyanate was 8 to 11 mg. per 100 c.c. of serum. Failure meant either that the blood pressure did not fall or that the patient felt worse when it did.

METHOD

Studies of minute vessels, as outlined in Parts I and II, were made on fifty-eight persons with hypertension who were treated with potassium thiocyanate. The cutaneous lymphatic flow was measured in twenty-eight of these cases. The general procedure and the method of estimating the thiocyanate level in the blood have been previously reported.[2] Blood volume was measured only in cases in which hospitalization was required. In these cases the patients were likely to have more severe symptoms, and be more ill, than those who were treated in the dispensary. Therefore, the blood volume estimations cannot be considered representative of the entire group. The blood volume was measured in only twelve cases. The amount of antidiuretic substance in the blood was measured in a few cases, as described in Part V. Since this test has been developed just recently, it was used in only a few new cases, and in old cases in which thiocyanate had had no effect.

RESULTS

The results are charted in Fig. 1. From such a small series absolute conclusions cannot be drawn. However, certain trends are apparent. A successful result is obtained more often when the minute vessel pressure is normal than when it is elevated. Furthermore, sclerosis of the precapillary arteriole (defined in Part II as failure of minute vessel pressure to change more than 3 mm. after the injection of histamine) or diminished (occasionally moderate) capillary mobility lessens the

likelihood of a good response.   An increase in cutaneous lymphatic flow is probably even more important in prognosis, for only one of eight responded favorably to thiocyanate, and that one had a normal minute vessel pressure!   Unfortunately, the protein content of the plasma in that case was not measured.

Eleven patients who had hypertension with papilledema (choking of one diopter, or more) were treated, without effect either on the blood pressure or the papilledema.   This is probably significant.
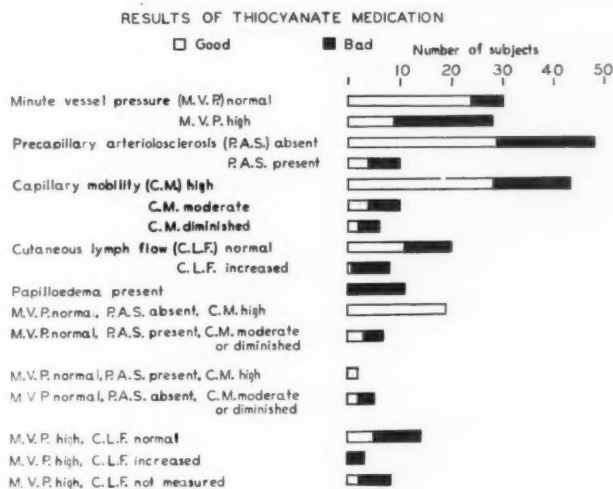

Fig. 1.—For details, see text.

Nineteen persons with normal minute vessel pressure and normal reactions to histamine were treated successfully.   The cutaneous lymphatic flow was normal in all of the cases of this group in which it was measured except one, as previously mentioned.   The results in this group are probably also significant, but it should be stated that the patients in this group had few or no symptoms in the beginning and, therefore, did not notice the therapeutic success.

In the group in which there was an elevation of minute vessel pressure, or precapillary arteriolar sclerosis, or diminished capillary mobility, or all three, the results were more or less variable.   The majority failed to respond to thiocyanate therapy.   However, some of the best symptomatic results in the entire group occurred in certain of these patients who did respond with a fall in pressure.   On the other hand, five such patients were made definitely worse by the treatment.

Thiocyanate was given to a number of negroes, some of whom responded well, and some did not.   As a rule, the tests as outlined cannot be applied to them because of the cutaneous pigmentation.   However, capillaries can be visualized occasionally in the negro, and, in a greater number, the spread of patent blue can be followed.

DISCUSSION

This will deal with (1) toxic effects, (2) effect on symptoms, and (3) relation to the tests and studies described in Parts I to V.

(1) *Toxic Effects.*—True toxic thiocyanate effects of any severity should never occur if the treatment is under proper control. One occasionally observes dermatitis or diarrhea as a manifestation of drug idiosyncrasy. Nausea and vomiting can usually be avoided by giving the drug in dilute solution. A certain degree of lassitude is sometimes noted as the blood pressure starts to fall. Nervousness and a sense of exhaustion occur occasionally when the blood level reaches 13 to 15 mg. per cent. In this study the highest blood level observed was 17 mg. per cent, so that the more marked toxic effects described by Barker[1] and others were not seen.

(2) *Effect on Symptoms.*—In five cases in which the treatment was regarded as a failure, there were symptoms which should perhaps be ascribed to the lowered blood pressure rather than to thiocyanate toxicity. These symptoms occurred when the thiocyanate content of the blood was not above therapeutic levels and coincidentally with the fall in pressure. Such symptoms included faintness, dizziness, syncope, and mental confusion. Possibly these patients had a disproportionate degree of sclerosis of the cerebral vessels. If cerebral vessels were unable to dilate, a high pressure might be required to maintain the cerebral capillary circulation.

Patients with renal insufficiency eliminate thiocyanate more slowly and are likely to require smaller doses. The renal status may change suddenly, and, if the dosage is not properly regulated, complications may ensue. For example, a patient who had been well controlled for $1\frac{1}{2}$ years on a constant dose was hospitalized for cystoscopic study. Catheterization of the left ureter caused some trauma and pain, but no other obvious untoward effects. One day later the patient felt rather weak, and her blood pressure was found to be 120; her usual pressure under treatment had been 150. Her blood thiocyanate level, which one week before had been 10 mg. per cent, was 17 mg. per cent. The dosage had not been changed. Administration of the drug was stopped, and two days later the blood level was still 14 mg. per cent. She recovered, and, eventually, after the usual dose had been resumed, the thiocyanate concentration in her blood returned to its original level. A fatal accident might perhaps have resulted if the administration of the drug had been continued uninterruptedly.

(3) *Relation to Special Tests and Studies.*—If arterial hypertension is not to affect the minute vessels, there must be some increase in the arteriolar barrier, i.e., the arterioles must be narrowed either by spasm or organic change. If the arteriolar contraction is primary, the arterial hypertension is secondary and compensatory, in that it is necessary to maintain the capillary circulation. If general vascular hypertension

(as opposed to mere arterial hypertension) is primary, e.g., as a result of failure to eliminate fluid at the same rate at which it is absorbed, arteriolar constriction might be regarded as compensatory, preventing an excessive increase of pressure in the capillaries and excessive loss of fluid into the tissues.

It is probable that thiocyanate relaxes arteriolar spasm. In partial support of this is the observation that occasionally a patient who responds successfully to thiocyanate may develop an increase in cutaneous lymphatic flow. Therefore, thiocyanate should fail, theoretically, if the narrowing is caused by organic change, or if the spasm is itself compensatory, or if the spasm is too strongly maintained.

The actual observations tend to support this hypothesis. Minute vessel sclerosis is frequently present when the treatment fails. That this is not always the case may mean that the cutaneous vascular area does not always behave like other vascular areas. Arteriolar spasm may be regarded as compensatory if there is an increased cutaneous lymphatic flow with no lowering of serum protein. This agrees with the few observations which are available, and with the experimental data charted in Fig. 2 of Part III. The degree of maintenance of the arteriolar spasm may possibly be estimated from the magnitude of the rise in pressure after administering histamine. In a few cases in which the minute vessel pressure was elevated, histamine produced a further rise of as much as 20 mm. of mercury, as shown in Fig. 4 of Part II. In such cases there was no response to thiocyanate, which may be unable to relax the intense spasm.

SUMMARY

The administration of thiocyanate is most likely to be efficacious in the treatment of hypertension if the minute vessel pressure is normal and the capillary count and minute vessel pressure react normally to histamine. Any variation from the normal response to the various tests which we employed makes success less likely. The treatment is least likely to succeed when an elevated minute vessel pressure is associated with increased cutaneous lymph flow, or when papilledema is present.

REFERENCES

1. Barker, M. H.: The Blood Cyanates in the Treatment of Hypertension, J. A. M. A. **106:** 762, 1936.
2. Griffith, J. Q., Jr., and Lindauer, M. A.: Thiocyanate Therapy in Hypertension, Including a New Micromethod for Determining Blood Thiocyanates, AM. HEART J. **14:** 710, 1937.

STUDIES OF CRITERIA FOR CLASSIFICATION OF ARTERIAL HYPERTENSION

VII. INCREASED INTRACRANIAL PRESSURE AND PAPILLEDEMA

J. Q. GRIFFITH, JR.,* M.D., W. E. FRY, M.D., AND E. ROBERTS, M.D.
PHILADELPHIA, PA.

NUMEROUS writers, including Shelburne, Blain, and O'Hara,[1] Masserman,[2] and Riser, Planques, and Barbier,[3] have speculated upon the interrelation between increased intracranial pressure, papilledema, and hypertension. It is generally agreed that increased intracranial pressure and papilledema usually occur together. However, their relation to the elevated blood pressure is not clear.

METHOD AND MATERIAL

During the course of the clinical studies described in the previous papers of this series, twenty-five persons who had both hypertension and papilledema were observed. The cerebrospinal fluid pressure was measured directly in most of these cases, and was found to be elevated. On all of these subjects some of the studies described in Parts I through V, including capillary counts before and after giving histamine and measurements of cutaneous lymphatic flow, blood volume, and the amount of antidiuretic substance in the serum, were made. Not all of the procedures were carried out in every case because (1) some of the subjects were negroes, whose cutaneous pigmentation interfered with the capillary studies; (2) some of the patients were studied prior to the development of certain of the tests; and (3) it was considered inadvisable to measure the blood volume in some cases.

RESULTS

1. Capillary mobility (as described in Part I). Capillary counts before and after the administration of histamine were made in sixteen cases. Capillary mobility was moderate in six, diminished in two, and high in eight.

2. Minute vessel pressure. This was measured in twenty-three cases, and found to be increased in twenty-one and normal in only two. The range was from 15 to 50 mm. of mercury, the average, 34. The effect of histamine was studied in seventeen instances. In five of these there was no significant change (less than 3 mm. of mercury), and, in the remainder, there were changes of 4 to 17 mm.

3. Cutaneous lymphatic flow was measured in fifteen cases. It was found to be increased in fourteen and normal in only one. One of the two subjects with normal minute vessel pressure and papilledema was found to have an increased cutaneous lymphatic flow; in the other the

latter was not measured. The one patient with papilledema and a normal cutaneous lymphatic flow had an increased minute vessel pressure.

4. Blood volume was measured in fourteen cases. It was elevated in twelve and ranged from 80 to 108 c.c. per kilogram of body weight, with an average of 89 c.c. In two instances it was normal (62 and 72 c.c. per kilogram of body weight, respectively). In one of these cases there was no change in capillary count or pressure after histamine; this indicates a rather indistensible vascular bed. On the other patient, a negress, capillary studies could not be made.

5. The blood was examined for antidiuretic substance in fourteen cases. It was absent in seven cases and present in seven.

DISCUSSION

In the absence of a mass lesion of the brain, an increase in intracranial pressure may occur under the following conditions: (1) If there is so much increase in the formation of cerebrospinal fluid that absorption becomes inadequate, cerebrospinal fluid pressure will rise until an equilibrium is established, either by reducing further formation, or increasing absorption, or both. (2) If the absorption of cerebrospinal fluid into the blood stream or lymphatic system is decreased, cerebrospinal fluid pressure will rise until an equilibrium is established, either by reducing cerebrospinal fluid formation to a point below normal, or increasing absorption somewhat, or both. These possibilities will be considered separately.

In a previous series of articles,[4, 5, 6, 7] evidence concerning the mechanism of the production of papilledema was presented. This evidence suggested that papilledema could not occur in the absence of a patent space along the optic nerve, extending from, and in communication with, the cerebrospinal space. As the perineural, and probably perivascular, spaces function in the so-called ''lymphatic'' absorption of cerebrospinal fluid, the occurrence of papilledema means that the route of lymphatic absorption is not blocked.

There is no direct evidence to indicate that there is or is not interference with the absorption of cerebrospinal fluid into the blood stream in such cases.

There is direct evidence that there is an increased formation of cerebrospinal fluid. The evidence may be presented as follows:

1. In the experimental animal, when fluid enters the blood stream in such large amounts that it cannot be immediately excreted through the kidneys, or when elimination of smaller amounts of fluid is interfered with by some antidiuretic agent, hypertension has been shown to occur,[8, 9] and is associated with increased blood volume and increased intracranial pressure. The evidence seems to warrant the assumption that the increased intracranial pressure in such animals is caused by an increased formation of cerebrospinal fluid.

2. Clinically, papilledema occurs in association with hypertension in those cases in which there seems to be difficulty in eliminating fluid from the blood stream, either because an antidiuretic substance is present, or because of renal failure. In such cases there is a tendency toward increased minute vessel pressure, increased cutaneous lymphatic flow (showing increased loss of fluid from the capillaries), and elevated blood volume. These factors, if they were operating within the cerebrospinal space, would tend to produce edema of the brain and increased cerebrospinal fluid formation. Papilledema itself is probably nothing more than evidence of increased transfer of fluid from the cerebrospinal space along the perineural space of the optic nerve. To this may be added the effect of increased pressure on the central vein of the retina where it passes through this space.

If increased cerebrospinal fluid pressure is simply the intracranial concomitant of increased loss of fluid from the capillaries everywhere, one might expect it to occur in all persons with elevated minute vessel pressure and increased cutaneous lymphatic flow. Such is not the case. The explanation may be that (1) the tests, as outlined, are not capable of detecting quantitative differences sufficient to distinguish between patients who will, and patients who will not, develop papilledema; and (2) the cutaneous and intracranial circulation may share to a different extent in the general disease process. For example, if arteriolar spasm is more strongly maintained in the intracranial area than in the skin, the loss of fluid into the brain would be less than into the skin.

The disappearance of papilledema in two cases after pituitary irradiation may, of course, have been merely coincidence and spontaneous regression, but the more likely explanation is that excretion of fluid through the kidney was made easier as the antidiuretic substance disappeared, and hence the formation of cerebrospinal fluid was decreased.

SUMMARY

Increased intracranial pressure and papilledema occur in those cases of hypertension in which, as a rule, minute vessel pressure, cutaneous lymphatic flow, and blood volume are increased. In certain cases, such abnormalities are associated with the presence of an antidiuretic substance in the blood which is, perhaps, derived from the pituitary. In other cases there is renal disease. The evidence strongly supports the suggestion that the increased cerebrospinal fluid pressure is caused by increased cerebrospinal fluid formation. The evidence is definitely incompatible with the idea that papilledema is caused by diminished absorption of cerebrospinal fluid into the lymphatic system. The evidence neither favors nor opposes the possibility that there may be decreased absorption into the blood stream.

REFERENCES

1. Shelburne, S. A., Blain, D., and O'Hara, J. P.: Spinal Fluid in Hypertension, J. Clin. Investigation 11: 489, 1932.
2. Masserman, J. H.: Cerebrospinal Hydrodynamics; Correlations of Pressure of Cerebrospinal Fluid With Age, Blood Pressure, and Blood Index, Arch. Neurol. & Psychiat. 34: 564, 1935.
3. Riser, J., Planques, and Barbier, Paulette: Cranial Hypertension in Relation to Arterial Hypertension, Presse méd. 47: 649, 1939.
4. Griffith, J. Q., Jr., Jeffers, W. A., Fewell, A. G., and Fry, W. E.: A Study of the Communication and Direction of Flow Between Cerebrospinal Fluid and Optic Discs in the Rat, Am. J. Ophth. 20: 457, 1937.
5. Jeffers, W. A., Griffith, J. Q., Jr., Fry, W. E., and Fewell, A. G.: An Experimental Study of Choked Disc in the Rat, Am. J. Ophth. 20: 881, 1937.
6. Griffith, J. Q., Jr., Jeffers, W. A., and Fry, W. E.: Papilloedema Associated With Subarachnoid Hemorrhage. An Experimental and Clinical Study, Arch. Int. Med. 61: 880, 1938.
7. Griffith, J. Q., Jr., Fry, W. E., and McGuinness, A.: Experimental and Clinical Studies in Hydrocephalus, Am. J. Ophth. 23: 245, 1940.
8. Griffith, J. Q., Jr., Jeffers, W. A., and Lindauer, M. A.: Transient Hypertension in Rats Following the Extravascular Administration of Fluid, Am. J. Physiol. 118: 1, 1937.
9. Griffith, J. Q., Jr.: Studies in Blood Volume and Blood Pressure Following the Extravascular Administration of Fluid in Rats, Am. J. Physiol 122: 140, 1938.

TREATMENT OF CONGESTIVE HEART FAILURE WITH AN ORALLY ADMINISTERED MERCURIAL DIURETIC

ROBERT C. BATTERMAN, M.D., ARTHUR C. DEGRAFF, M.D., AND
O. ALAN ROSE, M.D.
NEW YORK, N. Y.

ALTHOUGH the mercurial diuretics are unquestionably more effective when given parenterally than by any other route, the need for a potent diuretic which would require no special apparatus or procedure for its administration is evident. To the ambulatory patient who must have a diuretic frequently in order to remain free of edema, as well as to patients who are obese or have thrombosed veins, a mercurial diuretic which could be taken in some way other than by injection would be a boon. These considerations led to the development of mercurial suppositories as diuretic agents, and also prompted restudy of the oral administration of mercurial diuretics. Our remarks will be confined to the latter, for adequate observations on the suppositories are already available.

Calomel, advocated by Jendrassik,[1] in 1886, for the treatment of edema, was not only the first mercurial used for this purpose but also the first of its kind to be administered orally. The method of dosage, however (small amounts at frequent intervals), was somewhat hazardous, for it depended on the accumulation of sufficient mercury in the kidneys to initiate a diuretic action. Not only was the diuresis often unsatisfactory, but poisoning frequently occurred. Novasurol and salyrgan, when given orally, have little, if any, diuretic action.[2] As is the case with calomel, their mercurial fractions are altered by protein or the products of protein digestion within the gastrointestinal tract,[2b, 2d] so that the amount of absorption and, therefore, of diuresis is unpredictable. In addition, these compounds produce local irritating effects on the stomach and intestine which may result in ulceration or enterocolitis.[3]

In recent years the favorable influence of theophylline upon the diuretic effect and toxicity of mercurial diuretics which are administered parenterally has been established.[4] This fact prompted the observations of Chrometzka[5] and Görl[6] upon the oral use of such a combination. These authors reported favorably as to its effectiveness and safety. Their methods of study, i.e., using multiple doses for a period of a few days or weeks, do not permit, however, an adequate comparison with preparations which are given parenterally. Furthermore, evidence for their conclusion that the orally administered diuretic is milder and

has a more prolonged action than those which are given intravenously is lacking. A study was therefore planned so that the diuretic effectiveness of oral, in contrast to parenteral, administration could be more accurately evaluated in the treatment of congestive heart failure.

METHOD

A single dose of five tablets of salyrgan-theophylline* was given; each tablet contained 80 mg. of salyrgan (30 mg. of mercury) and 40 mg. of theophylline. The effectiveness and toxicity of this procedure were compared with the results of administering 1 or 2 c.c. of salyrgan-theophylline or mercupurin intravenously (mercury content approximately 40 mg. per c.c.). Forty-eight patients were studied; twenty-nine received the tablets; twenty-four, salyrgan-theophylline intravenously; and thirty, mercupurin intravenously. In twenty-two instances it was possible to compare the diuretic effect of the two methods of administration in the same patient.

The general plan of study for all mercurial diuretics has been previously reported in detail.[4a, 7] The salient features are, in brief, as follows. The diuretics were administered after a preliminary control period, during which the maximum effect of absolute rest in bed, oxygen, sedatives, limitation of fluid intake, dietary restrictions, ammonium chloride, and digitalis was ascertained. The dose of ammonium chloride, when it was used, was 1 to 2 Gm. three times a day. The urine was examined at frequent intervals for albumin and formed elements. When more than one diuretic was studied, the patient's weight was allowed to become constant or to return to the initial level before the second drug was given. The weight curve was found to be a more accurate index of the diuretic effect than the urinary output, because the latter tended to fluctuate widely. The weight was also a good guide to the amount of fluid available in the body for diuresis. A loss of 3 pounds, or more, in body weight within forty-eight hours of the administration of the diuretics was considered significant.

RESULTS

In a group of nine patients (Table I), the tablets were given whenever a diuretic was considered to be necessary, usually at intervals of three to five days. A satisfactory effect was obtained in all but one instance (third trial, No. 24), but even in this case further administration of the diuretic resulted in a good response. In two cases the tablets were administered four times, and, in one case, five times, without evidence of toxicity.

The effectiveness of the oral preparation was also compared with that of other diuretics (Table II). The results of using suppositories, which were obtained during a previous study,[7] are included. In approximately 72 per cent of the fifty-six trials with the salyrgan-theophylline tablets on twenty-nine patients a satisfactory diuresis was produced. The parenteral preparations were more consistently effective; they produced diuresis in approximately 90 to 95 per cent of the cases. It is also evident that the oral preparation of salyrgan-theophylline is more likely to cause satisfactory diuresis than the suppositories, which have an effectiveness of 50 to 63 per cent (Fig. 1).

*Salyrgan-theophylline in enteric coated tablets (research number S. T. O. 3813) and in 1 c.c. ampules (research number S. T. 3833) was supplied by the Winthrop Chemical Company, Inc.

From a study of the number of trials (Fig. 2) which produced a definite diuresis, it is clear that oral administration causes a loss of 3 to 5 pounds in body weight; occasionally, the loss exceeds 8 pounds. The parenteral preparations, on the other hand, produce a greater diuresis, and weight losses of more than 8 pounds are common.

TABLE I

DIURETIC EFFECTIVENESS OF SALYRGAN-THEOPHYLLINE, ADMINISTERED ORALLY

NO.	DIURETIC	DATE	NH$_4$Cl	INITIAL WEIGHT (LB.)	WEIGHT FIRST DAY (LB.)	LOSS FIRST DAY (LB.)	MAXIMUM LOSS (LB.)	DAYS
5	5 Tablets STO*	12/ 1/39	3	179	177	2	3	2
	5 Tablets STO	12/ 4/39	3	176½	172¾	3¾	7	3
	5 Tablets STO	12/14/39	3	163¼	159½	3¾	3¾	1
	5 Tablets STO	12/20/39	3	156½	154	2½	5½	2
11	5 Tablets STO	8/28/39	3	167	163½	4½	13	3
14	5 Tablets STO	9/13/39	3	215	212½	2½	10	3
20	5 Tablets STO	11/ 4/39	3	148½	144	4½	4½	1
	5 Tablets STO	11/ 7/39	3	143½	138	5½	5½	1
	5 Tablets STO	11/10/39	3	138	136¾	1¼	5	3
22	5 Tablets STO	11/13/39	3	141½	139	2½	3½	2
23	5 Tablets STO	11/17/39	3	149¾	144	5¾	8¼	3
	5 Tablets STO	11/21/39	3	141	134	7	8½	3
24	5 Tablets STO	12/ 2/39	3	168½	161½	7	9¾	2
	5 Tablets STO	12/ 8/39	3	156½	150	6¼	6½	1
	5 Tablets STO	12/12/39	3	150¼	148	2¼	2¼	1
	5 Tablets STO	12/15/39	3	148	144½	3½	3½	1
	5 Tablets STO	12/19/39	3	144½	138	6½	6½	1
25	5 Tablets STO	12/11/39	3	154¾	148¼	6¼	6¼	1
	5 Tablets STO	12/15/39	3	148½	145¼	3	3	1
26	5 Tablets STO	12/ 9/39	3	181½	174	7½	7¼	1
	5 Tablets STO	12/13/39	3	174½	166½	8	11	3
	5 Tablets STO	12/18/39	3	163	156¼	6¾	6¾	1
	5 Tablets STO	12/21/39	3	159	150½	8¼	8½	1

*Enteric-coated salyrgan-theophylline preparation.

TABLE II

COMPARATIVE EFFECTIVENESS OF MERCURIAL DIURETICS WHEN ADMINISTERED BY THE ORAL, PARENTERAL, AND RECTAL ROUTES

DIURETIC	NO. OF TRIALS	TRIALS SUCCESSFUL		NO. OF PATIENTS	PATIENTS SUCCESSFULLY TREATED	
		NO.	PER CENT		NO.	PER CENT
Salyrgan-Theophylline by mouth (5 tablets)	56	40	71.5	29	22	75.8
Salyrgan-Theophylline intravenously	37	35	94.6	24	23	95.8
Mercupurin intravenously	60	55	91.7	30	29	96.6
Mercurin suppository	22	14	63.6	13	6	46.1
Salyrgan (modified) suppository	20	10	50.0	11	8	72.7

Although the onset and peak of diuresis after oral administration occurred slightly later than after parenteral injection, the diuresis was, in the majority of cases, complete within twenty-four hours. However, in 35 per cent of the trials a significant weight loss occurred within the second twenty-four hours.
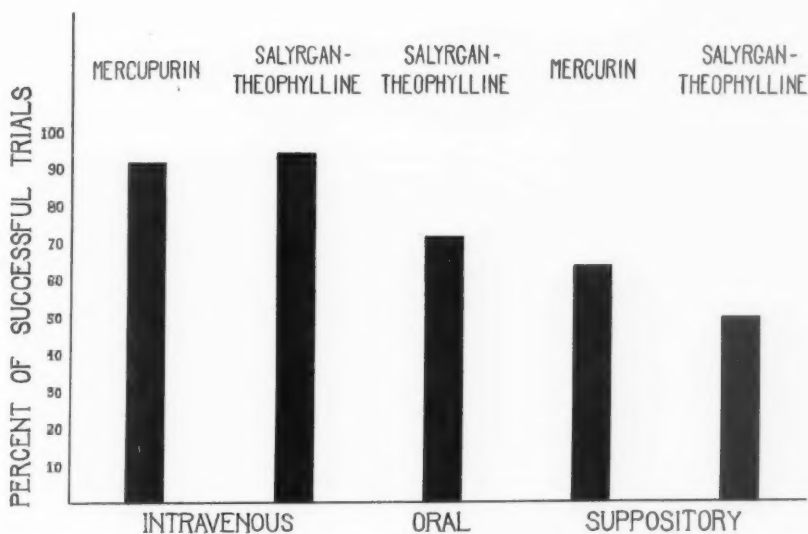
Fig. 1.—Comparative effectiveness of mercurial diuretics when administered by the intravenous, oral, and rectal routes.
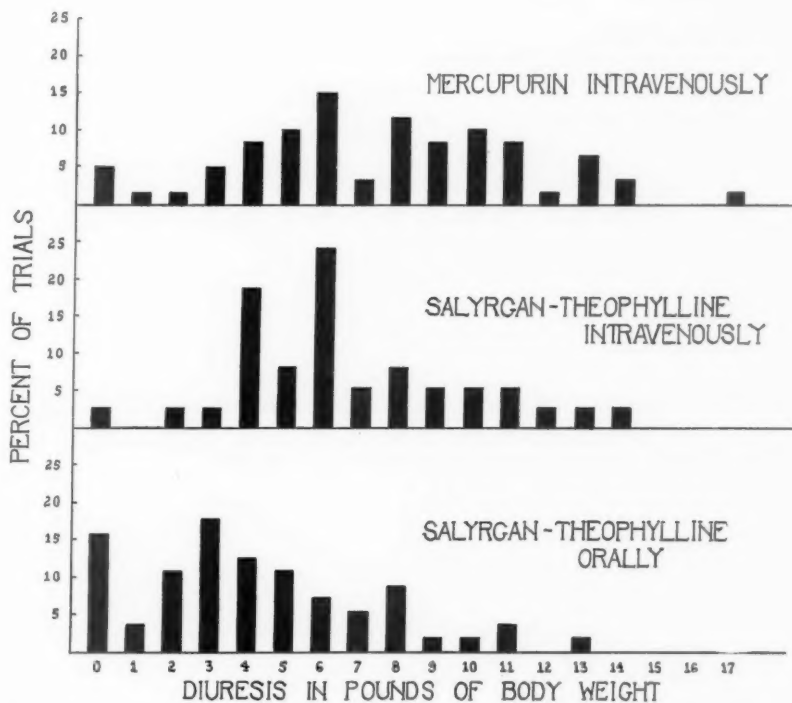

Fig. 2.—Degree of diuresis, as judged by weight lost, obtained by giving salyrgan-theophylline orally, and mercupurin and salyrgan-theophylline intravenously.

The oral preparation failed to elicit a satisfactory response in sixteen instances, but in eight of these it was successful at other times. As was the case with the parenteral preparations, the previous administration of ammonium chloride and digitalis increased the effectiveness of the oral preparation. Although in several cases there was no apparent reason for failure, in others it appeared to be related to the advanced state of heart disease and lack of digitalis or of ammonium chloride.

Three patients experienced gastrointestinal symptoms after taking the tablets of salyrgan-theophylline. Two had diarrhea, and the other had epigastric discomfort, but in each case subsequent administration of the oral preparation was well borne. With the doses used, none of the patients showed any signs of renal irritation.

DISCUSSION

With the introduction of the oral preparation, four routes (intravenous, intramuscular, rectal, and oral) are now available for the administration of mercurial diuretics to patients with the edema of congestive heart failure. The modes of administration are not, of course, interchangeable to the extent that a satisfactory and comparable diuresis is obtained in every instance without regard to the preparation used or the state of the patient; one should select the method of administration which best suits the needs of each patient. The parenteral preparations are still the ones of choice whenever a rapid and marked diuresis is desired. They are, therefore, most suitable in cases of acute congestive heart failure, when immediate results are desired. For the patient with edema who is not acutely ill and does not require drastic measures for symptomatic relief, the oral preparation, because of its safety and efficacy, is suggested as the diuretic of choice. The unreliability of the mercurial suppository and the fact that it frequently causes rectal irritation[7] limit its usefulness. However, suppositories may occasionally be used to advantage when the patient cannot tolerate the oral preparation, or when there are contraindications or objections to parenteral administration.

The single dose of five tablets of salyrgan-theophylline (equivalent to 150 mg. of mercury) is by no means the dose recommended for all patients, but, when massive edema is present, it appears to be very satisfactory. For the ambulatory patient with a minimal amount of heart failure, this dose may be excessive. Therefore, further observations are now being made in order to ascertain the proper dose for prolonged treatment.

Gastrointestinal irritation occurs occasionally, and perhaps dividing the dose or giving a smaller one might result in diuresis without producing this untoward effect. Preliminary observations on animals have failed to reveal significant gastrointestinal irritation with doses several times as large as those used therapeutically. However, only studies on

ambulatory patients or patients with chronic congestive heart failure, over an extended period of time, will answer the question whether repeated use of the oral preparation is safe.

CONCLUSIONS

1. Salyrgan-theophylline, when administered orally in doses equivalent to 150 mg. of mercury, is an effective and safe diuretic.

2. The diuresis is not only slower in its onset, but also more prolonged than after parenteral administration.

3. The diuretic effect is less than that produced by the parenteral preparations, but greater than with the suppositories.

REFERENCES

1. Jendrassik, E.: Kalomel als Diuretikum, Deutsches Arch. f. klin. Med. **38:** 499, 1886.
2. (a) Saxl, P.: Über perorale Novasuroltherapie, Wien. klin. Wchnschr. **39:** 816, 1926.
   .(b) Engel, K., and Epstein, T.: Die Quecksilberdiurese, Ergebn. d. inn. Med. u. Kinderh. **40:** 187, 1931.
   (c) Engel, K.: Über die Ausscheidung des Quecksilbers nach der Andwendung von Novurit, Orvoskepzes (Supplement, Aerztliche Fortbildung) **24:** 29, 1934.
   (d) Engel, K.: A Novurilkupókról, Orvosi hetil. **78:** 940, 1934.
3. Unpublished data.
4. (a) DeGraff, A. C., Nadler, J. E., and Batterman, R. C.: A Study of the Diuretic Effect of Mercupurin in Man, Am. J. M. Sc. **191:** 526, 1936.
   (b) DeGraff, A. C., and Batterman, R. C.: Reaction at Site of Injection of Mercurial Diuretics as Influenced by Theophylline, Proc. Soc. Exper. Biol. & Med. **32:** 1546, 1935.
   (c) DeGraff, A. C., Batterman, R. C., and Lehman, R. A.: Limiting Content of Theophylline Necessary to Prevent Local Toxic Action of Mercurial Diuretics, Proc. Soc. Exper. Biol. & Med. **38:** 373, 1938.
5. Chrometzka, F.: Die diuretische Wirkung peroral gegebenen Salyrgans, Fortschr. d. Therap. **15:** 87, 1939.
6. Görl, P.: Zur peroralen Salyrgan-Therapie, Med. Klin. **35:** 578, 1939.
7. Brightman, I. J., and Batterman, R. C.: The Treatment of Edema by Rectal Administration of Diuretics, J. Lab. & Clin. Med. **25:** 1038, 1940.

ELECTROCARDIOGRAPHIC OBSERVATIONS ON ATHLETES BEFORE AND AFTER A SEASON OF PHYSICAL TRAINING

W. W. TUTTLE, PH.D., AND HORACE M. KORNS, M.D.
IOWA CITY, IOWA

THERE have been many electrocardiographic studies of the effects of exercise, but most of them have dealt with either the acute or remote chronic effects. In this investigation an attempt was made to detect any electrocardiographic changes which might be brought about by an entire season of physical training and athletic competition. The study was undertaken because of the frequent and persistent inquiries concerning the possibility that the heart may be injured by the rather long periods of sustained exertion which are required in the preparation for athletic competition.
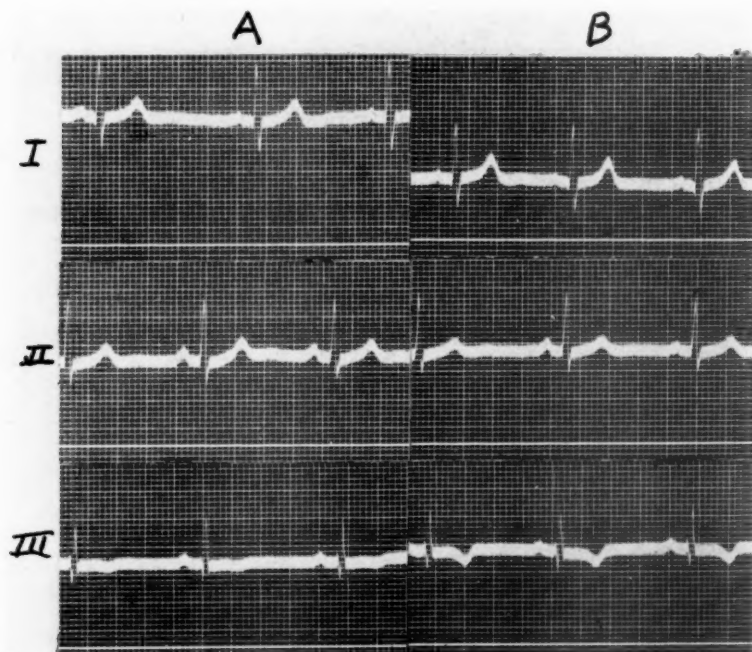
Fig. 1.—E. Mc., aged 20 years, gymnast. *A*, before training. *B*, after training. Leads I and II did not change, but in Lead III the T wave became much more definitely inverted.

Kraus and Nicolai[1] found that the electrocardiograms of trained athletes, at rest, were practically the same as those of untrained subjects, except that the T wave tended to be higher. Messerle[2] reported that training not only caused the T wave to become higher, but lowered the

ventricular peaks and greatly increased the duration of QRS. These variations were attributed to vagal influence. It is generally recognized, of course, that physical training decreases the resting heart rate. Hoogerwerf[3] summed up the situation concerning the effects of exercise on the heart by saying that, although many changes take place during exertion, they are not peculiar to the physically trained person but occur in the case of the untrained subject, also.
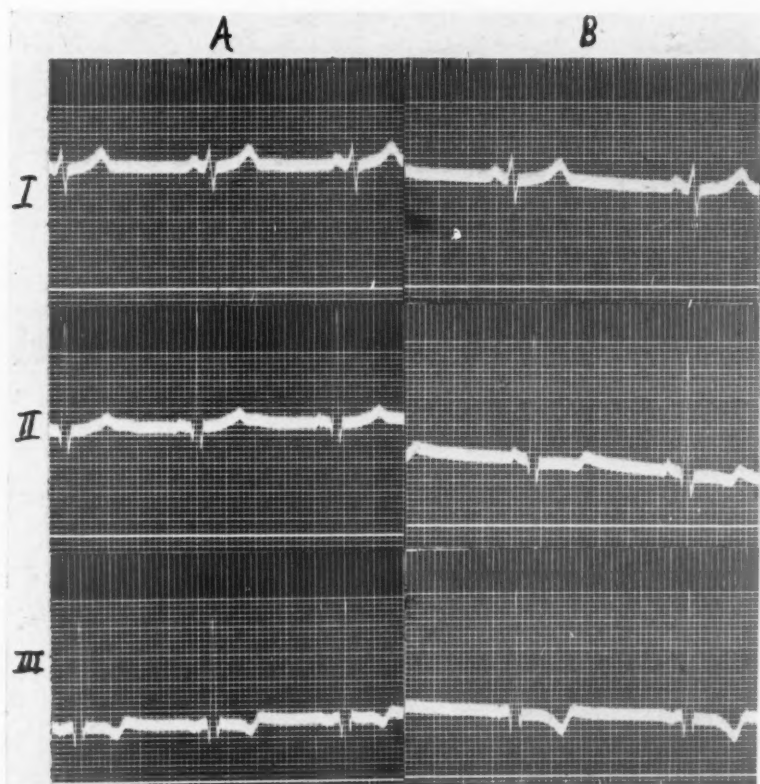

Fig. 2.—J. D., aged 21 years, basketball player. *A*, before training. *B*, after training. No change in Lead I. In Lead II the T wave became diphasic, and in Lead III the degree of inversion of the T wave increased.

Observations were made on forty-eight athletes, all of whom were healthy, normal, young men. There were four wrestlers, seven gymnasts, nine swimmers, six basketball players, and twenty-two track men. Each member of the group took part consistently in varsity competition. An electrocardiogram was made on each subject at the beginning of the training season, and again near the end, after strenuous training and active competition, when the men were in the pink of condition.

RESULTS

In forty-three cases there was no difference between the electrocardiograms which were made at the beginning of the training period and
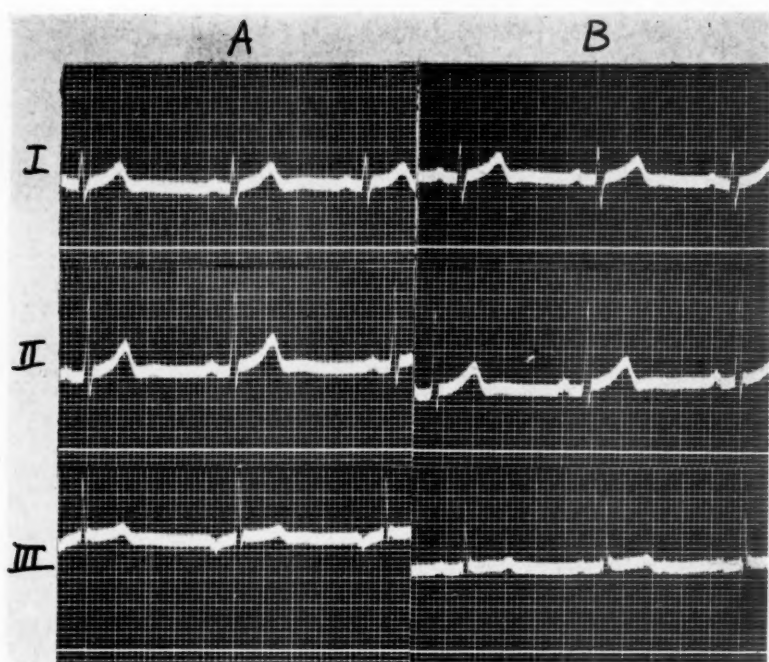
Fig. 3.—R. L., aged 20 years, swimmer. A, before training. B, after training. No change in Leads I and II. In Lead III, the P wave, which had been inverted, became upright.
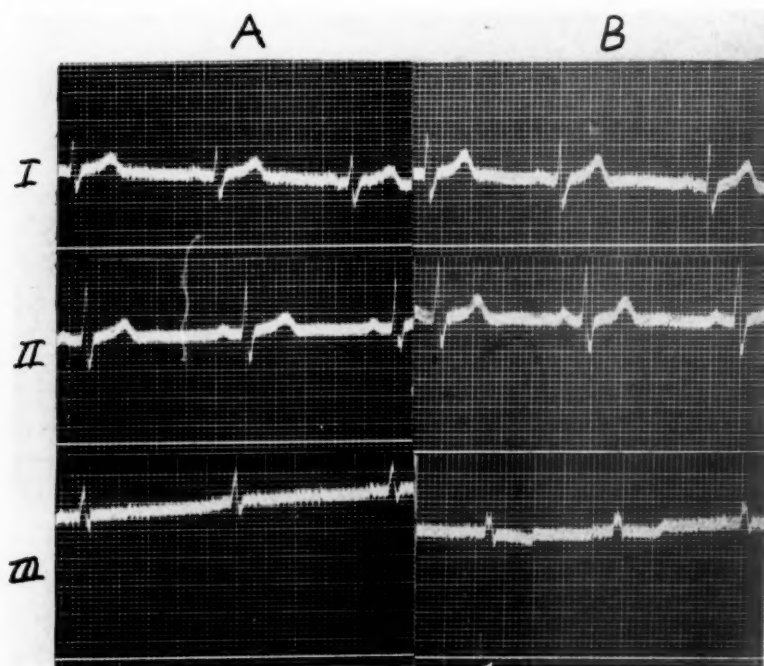

Fig. 4.—C. K., aged 21 years, wrestler. A, before training. B, after training. In Lead I the amplitude of the R and T waves increased slightly. No change in Lead II. In Lead III, the T wave, which had been isoelectric, became inverted.

those obtained when the men were at their peak. In one of the remaining cases the alterations were insignificant; the changes in the other four are depicted in Figs. 1, 2, 3, and 4.

CONCLUSIONS

Strenuous training and active competition produced slight electrocardiographic changes in four, or 8.3 per cent, of a group of forty-eight healthy young athletes. Although we have no explanation for these alterations, particularly those in the T wave, we have convinced ourselves that they were not indicative of myocardial injury. No two of these four men were engaged in the same sport.

REFERENCES

1. Kraus, F., and Nicolai, G.: Das Elektrocardiogramm des gesunden und kranken Menschen, Leipzig, 1910.
2. Messerle, N.: Die Veränderungen im Elektrokardiogramm bei Körperarbeit, Ztschr. f. d. ges. exper. Med. 60: 490, 1928.
3. Hoogerwerf, S.: Elektrokardiographische Untersuchungen der Amsterdamer Olympiadekämpfer, Arbeitsphysiol. 2: 61, 1929.

Department of Clinical Reports

ULCERATING VALVULAR LESIONS IN SUBACUTE BACTERIAL ENDOCARDITIS CAUSED BY THE STREPTOCOCCUS VIRIDANS

REPORT OF A CASE

ALFRED F. KNOLL, M.D.

PITTSBURGH, PA.

ULCERATING valvular lesions in subacute bacterial endocarditis are not commonly encountered, and, aside from the writings of Libman, have received scant recognition in the literature.

Twenty-eight years ago, Libman[1] stated that in subacute bacterial endocarditis "ulceration of the aortic valve at times occurs; ulceration of the mitral valve is rare." In 1923, Libman[2] reiterated that "if ulceration does occur in subacute cases it is usually in the aortic flaps."

Boyd,[3] like Libman, has seen "a number of cases of ulcerating valvular lesions in subacute bacterial endocarditis." These, however, were confined to the aortic cusps. He has not observed any ulcerating lesions on the mitral valve in this disease. Gault[4] also recalls having seen two similar cases which he explains as follows: "It would appear that in certain persons the degree of tissue sensitivity to the toxin varies, and when extreme allergy is present, necrosis may be an important part of the lesion, with subsequent ulceration." Clawson[5] considered that the type of endocarditis is determined less by the kind of organism and more by its virulence.

In light of the above comments, the following case is reported.

REPORT OF A CASE

W. W., a white man, aged 22 years, was admitted to the medical service of Dr. H. E. Waxman, at The Western Pennsylvania Hospital, Aug. 25, 1938, complaining of fever, chills, perspiration, and "a cold."

The patient gave a history of measles and chicken pox, as well as rheumatic fever at the age of four years. Because of frequent attacks of tonsillitis, the tonsils were removed in 1935. The family history was irrelevant. The patient smoked twenty cigarettes daily, and used alcohol moderately. He denied having had venereal disease. He was employed as a "chipper" in a steel mill and had worked eight hours daily until several days before admission. The work of a "chipper" consists of removing the rough surfaces of castings and is considered rather heavy manual labor. He had been told of his "heart condition" five years previously. Palpitation had been experienced at times, and, in the preceding two months, there had been occasional attacks of mild precordial pain. Three weeks before admission he had had an attack of "grippe," and had not felt well thereafter.

He recalled seven definite occasions during that period when he had had attacks
of fever, preceded or followed by chills, and with pronounced sweating. Four of
these attacks occurred in the evening. He continued to work, but noticed pro-
gressive weakness and a weight loss of 20 pounds. Four days prior to admission
he contracted an upper respiratory infection which added to his discomfort.

On admission the patient was found to be well-developed, muscular, well-
nourished, and very pale. He lay comfortably in bed, although he appeared to
be quite ill. He was perspiring profusely. Herpes were present about the mouth
and nose. There were no conjunctival or cutaneous petechiae. Cardiac enlargement
to the left was demonstrated by percussion. The heart sounds were of poor quality;
at the apex there were an apical systolic and a diastolic murmur which were trans-
mitted to the left axilla. The pulmonic second sound was accentuated. The blood
pressure was 90/50. The abdomen was soft and full, and the spleen was palpable.
A provisional diagnosis of bacterial endocarditis was made, and daily intravenous
injections of sodium cacodylate (7.5 grains) were started and continued until the
eighteenth day.

A septic temperature curve, ranging from 97° to 103.3° F., continued throughout
the twenty-one days of hospitalization. The pulse rate varied from 64 to 112,
and the respiratory rate, from 18 to 22. Immunotransfusions (typhoid) of 400
to 500 c.c. of blood were administered on the sixth, ninth, thirteenth, and
seventeenth days. The last three transfusions were followed by chills. On admis-
sion the erythrocyte count was 4,410,000, and the hemoglobin, 85 per cent; on the
ninth day, the erythrocyte count was 4,150,000, and the hemoglobin, 80 per cent;
and on the twentieth day, the erythrocyte count was 3,060,000, and the hemoglobin,
60 per cent. The leucocyte counts on the same dates were 10,500, 7,700, and 21,100,
respectively. A trace of albumin was found in the urine on two occasions, but
there was no hematuria. A blood culture which was taken on admission showed
250 colonies of *Streptococcus viridans* per cubic centimeter; a second culture, six
days later, showed 275 colonies per cubic centimeter; and a third, on the fifteenth
hospital day, despite the intravenous medication, showed 285 colonies per cubic
centimeter. The patient grew worse rapidly.

On the eighteenth day, the administration of acetyl sulfone (4,4'-diacetyldia-
minodiphenylsulfone)* orally, in doses of one gram three times a day, was begun.
On the twenty-first day the patient died suddenly. A blood culture which was
secured twelve hours ante mortem, after the administration of 7 grams of acetyl
sulfone, exhibited twelve colonies of *Streptococcus viridans* per cubic centimeter,
and another, taken nine hours post mortem, showed only three colonies per cubic
centimeter. The appearance of growth in the last two cultures was delayed twenty-
four hours, as compared to the first three cultures. The organism was carefully
studied by Dr. Philip Hadley, who classified it as a *Streptococcus viridans*. No
hemolytic zone was evident on aerobic or anaerobic media, and the bacterium was
nonpathogenic for mice, rats, and guinea pigs. The virulence of the organism
could not be enhanced by more than six successive mouse passages.

POST-MORTEM EXAMINATION

The body was that of a well-developed man; it weighed about 165 pounds and
measured 175 cm. in length. The skin was moderately jaundiced. There were
a few herpes about the nares, and some conjunctival petechiae. The heart weighed
575 grams and showed pronounced hypertrophy of the left ventricle and dilatation
of all the chambers, particularly on the right side. The musculature of all of the
chambers was moderately hypertrophied; the left ventricular wall averaged 2 cm.
in thickness. The myocardium was reddish brown in color and soft in consistency.
The aortic valve was bicuspid; its leaflets were markedly thickened, distorted,
and adherent to each other. An aneurysmal pouching of the posterior cusp, with

*Kindly supplied by the Monsanto Chemical Company, St. Louis, Missouri.

an irregular, ragged perforation measuring 0.5 cm. in diameter, was covered by a large, soft, friable, irregular, mottled, red and gray vegetation measuring about 2 cm. in diameter (Fig. 1). No inflammatory changes were present on any of the other valves. Focal, embolic glomerulonephritis, acute hepatitis and hepatomegaly (2825 grams), septic splenitis and splenomegaly (600 grams), with infarction, bilateral bronchopneumonia, bilateral hydrothorax, hydroperitoneum (300 c.c.), and hydropericardium (250 c.c.) were the other significant abnormalities.
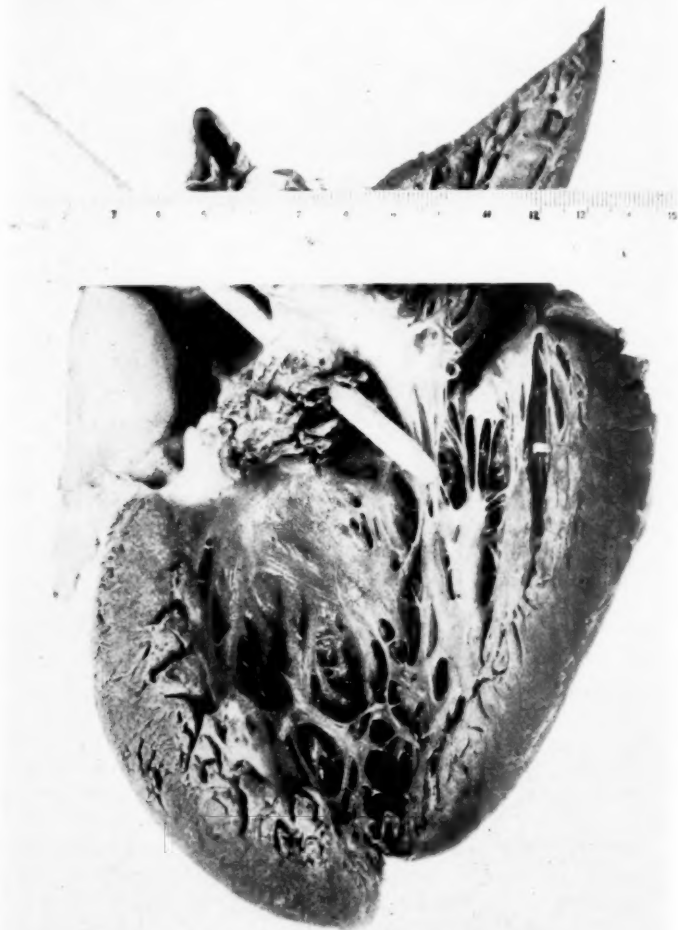

Fig. 1.—Photograph of fixed heart, showing a deformed, bicuspid, aortic valve, with a probe extending through a perforation of the posterior cusp. A large, friable mass of vegetations covers the posterior cusp and part of the adjacent cusp.

Microscopic Examination.—The vegetations, in general, were of two types, namely, very recent ones, which showed the classical combination of fibrin, erythrocytes, leucocytes, and some monocytes, and definitely older ones, characterized, in some instances, by highly cellular and vascular granulation tissue (Fig. 2), and, in others, by cellular fibrous tissue (Fig. 3) in which inflammatory cells and vessels were much less abundant. The older vegetations were covered by endothelium. In some regions the older vegetations were the seat of a fibrinoid necrosis

of variable depth.   This fibrinoid necrosis was also present in regions in which
the endocardium was composed of acellular, hyalinized collagen.   In addition to
the vegetations, there were, on the ventricular and aortic aspects of the cusps,
extensive subendocardial foci which showed extreme cellularity.   Most of these
cells were fibroblastic in type and were associated with many other mononucleated

Fig. 2.—Photomicrograph of vegetation, showing, in addition to marked cellularity, a
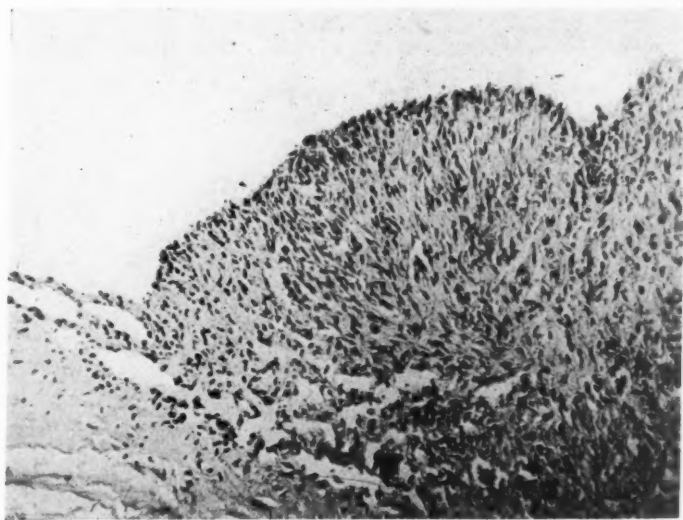high degree of vascularity indicative of early organization.   (H & E ×102.)

Fig. 3.—Photomicrograph of more advanced organization of a vegetation.   (H & E
×133.)

cells, but leucocytes were scanty.   Occasionally, foci which varied in size from
that of a half to several low-power fields contained leucocytes almost exclusively,
and, in a few areas, leucocytes and monocytes were present in equal number; but,
in general, mononucleated cells definitely outnumbered the others.   In the region
of the perforation there was a purulent necrosis which also involved the lower

portion of the sinus of Valsalva. A bacterial stain of the fresh vegetations showed
cocci arranged singly and in chains of three and four. The bulk of the aortic
valve consisted of acellular hyaline collagen and vascular fibrous tissue, with foci
of calcification. Some sections of myocardium showed diffuse infiltration by acute
inflammatory cells, frequent minute foci of necrosis, and occasional small accumula-
tions of leucocytes. Subacute and chronic perivascular inflammation and peri-
vascular fibrosis were often found. Petechiae, minute infarcts, and Aschoff bodies
were not conspicuous. Several small vessels contained partially organized thrombi.
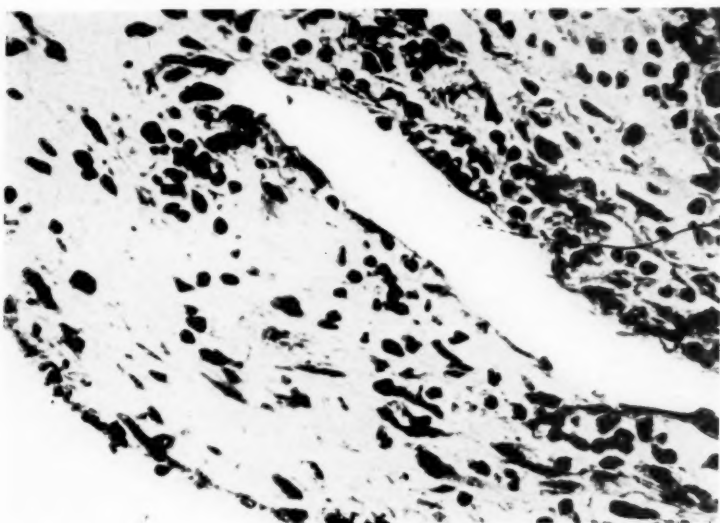The parietal endocardium showed moderate thickening and monocytic infiltration.

Fig. 4.—Higher magnification of granulation tissue seen in Fig. 2. (H & E ×382.)

DISCUSSION

In attempting to classify this case as one of subacute bacterial endo-
carditis, several pertinent features are to be considered. Microscopically,
various stages of organization were readily demonstrable in the vegeta-
tions. Of particular import was the presence of endocardial excrescences
composed of capillaries with swollen endothelial cells, young, plump
fibroblasts, and occasional monocytes and leucocytes in an edematous
fibrillar stroma, which is so characteristic of young granulation tissue
(Fig. 4). The five blood cultures, one of which was taken post mortem,
showed pure growths of *Streptococcus viridans*. Furthermore, focal,
embolic glomerulonephritis, which is associated exclusively with sub-
acute bacterial endocarditis, was present in this case. The myocardial
lesions were similar to those found by Saphir[6] in an analysis of thirty-
five cases of subacute bacterial endocarditis. Pyemic phenomena, which
are so commonly associated with acute ulcerative endocarditis, were
absent.

Against the diagnosis of subacute bacterial endocarditis were the very
bulkiness of the vegetations and a perforation of one of the cusps. It

is in reference to this perforation that the term "ulceration" has been used throughout this paper, and it should not be confused with the microscopic ulceration which is admittedly common in subacute bacterial endocarditis.[5]   As was mentioned previously, Libman,[1] Boyd,[3] and Gault[4] have pointed out that the macroscopic type of ulceration occurs in subacute bacterial endocarditis.

Acute bacterial endocarditis may at times present features which are ordinarily characteristic of the subacute variety.   Thus, Karsner[7] has seen evidence of organization in gonococcic and pneumococcic endocarditis when the duration of the disease was approximately three months.   Ribbert,[8] in 1924, stated that from the anatomic point of view there are two types of endocarditis, namely, the verrucose and the ulcerative, although a sharp borderline between the two does not exist. He pointed out that, clinically, a sharp differentiation is also impossible, because, at times, in cases of subacute bacterial endocarditis, one is not able to ascertain during the life of the patient what form of the disease will be encountered at autopsy.

It is generally considered that the duration of subacute bacterial endocarditis is in excess of six weeks; yet the patient under discussion apparently died within that period of time.   It must be remembered, however, that this subject was a robust, very muscular, hyposensitive person, and that therefore the duration of his illness was probably much longer than the history indicated.

Present-day treatment of this disease is just as varied as it is ineffective.   Capps[9] tabulated sixty-seven reported cures which lasted one year or more, and added seven more patients from his own series who survived more than five years.   Of the total of seventy-four cases, there was no specific therapy in twenty-nine, in eighteen the mode of treatment was not stated, and in the remaining twenty-seven cases various agents were used, including sodium cacodylate, vaccines, normal sera, salvarsan, radium, and immunotransfusions.

In evaluating any instance of recovery from subacute bacterial endocarditis, the deductions of Clawson and Bell[10] must be taken into consideration.   From a series of thirty-five cases of acute rheumatic fever and eighty cases of subacute bacterial endocarditis, they concluded that the coexistence of bacteriemia and endocarditis does not necessarily mean that the patient has what is clinically recognized as subacute bacterial endocarditis; and that the streptococcus, generally the viridans strain, seems to be responsible for both the rheumatic and subacute bacterial forms.

The drug (acetyl sulfone) which was administered in this case has been used to some extent in France for the treatment of gonorrhea.   Its action has been investigated by Cooper, Gross, and Lewis,[11] who found that it was more effective than sulfanilamide in the treatment of hemolytic streptococcic infections in animals.   In this case, coincident with

the medication, there was a marked diminution in the number of colonies of *Streptococcus viridans*, but bacteria were readily found in the vegetations. The employment of this drug in several other cases in this institution resulted only in a temporary decrease of the blood bacterial count.

In conclusion, the experiments of MacNeal and his associates,[12] in which vegetative endocarditis was produced in rabbits by repeated intravenous injections of serum-broth cultures of *Streptococcus viridans*, should be mentioned. Among the resultant lesions were various stages of growth and healing of vegetations. MacNeal[13, 14] feels that these lesions were identical with those of human subacute bacterial endocarditis. He[15] suggests that classification of diseases of the heart valves should be etiologic, and that, therefore, one should speak of a vegetative endocarditis caused by the *Streptococcus viridans*.

CONCLUSIONS

1. Perforation of the aortic valve in a case of subacute bacterial endocarditis caused by the *Streptococcus viridans* is reported.

2. The difficulty of classifying anatomic lesions under the heading of subacute bacterial endocarditis, in the light of expert opinion and recent experimental work, is discussed.

3. In this case, the administration of 4,4'-diacetyldiaminodiphenyl-sulfone was accompanied by a marked drop in blood bacterial content.

REFERENCES

1. Libman, E.: A Study of Endocardial Lesions of Subacute Bacterial Endocarditis With Particular Reference to Healing or Healed Lesions; With Clinical Notes, Am. J. Med. Sci. **144:** 313, 1912.
2. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80:** 813, 1923.
3. Boyd, W.: Personal communication.
4. Gault, E.: Personal communication.
5. Clawson, B. J.: An Analysis of 220 Cases of Endocarditis With Special Reference to the Subacute Bacterial Type, Arch. Int. Med. 33: 157, 1924.
6. Saphir, O.: Myocardial Lesions in Subacute Bacterial Endocarditis, Am. J. Path. **11:** 143, 1935.
7. Karsner, H. T.: Personal communication.
8. Ribbert, H.: Handbuch d. spez. pathol. Anat. u. Histol., 2, Henke, F., and Lubarsch, O., Berlin, 1924, Julius Springer.
9. Capps, J. A.: Subacute Bacterial Endocarditis Due to Streptococcus Viridans With Special Reference to Prognosis, Ann. Int. Med. **13:** (O. S. XVIII), 280, 1932.
10. Clawson, B. J., and Bell, E. T.: A Comparison of Acute Rheumatic and Subacute Bacterial Endocarditis, Arch. Int. Med. 37: 66, 1926.
11. Cooper, F. B., Gross, P., and Lewis, M.: Sulfone and Sulfonanilide Therapy in Streptococcal Infections, Proc. Soc. Exper. Biol. and Med. **38:** 375, 1938.
12. MacNeal, W. J., Spence, M. J., and Wasseen, M.: Transmission of Endocarditis Lenta to Rabbits, Proc. Soc. Exper. Biol. and Med. **40:** 473, 1939.
13. MacNeal, W. J.: Personal communication.
14. MacNeal, W. J., Spence, M. J., and Wasseen, M.: Experimental Production of Endocarditis Lenta, Am. J. Path. **15:** 695, 1939.
15. MacNeal, W. J., Spence, M. J., and Wasseen, M.: Transmission of Endocarditis Lenta to Rabbits, Am. J. Path. **15:** 602, 1939.

SYSTOLIC GALLOP RHYTHM AS A SIGN OF ANEURYSM OF THE LEFT VENTRICLE

REPORT OF A CASE*

GEORGE V. LeRoy, M.D., AND RALPH C. ROBERTS, M.D.†

CHICAGO, ILL.

SYSTOLIC gallop rhythms, when the extra sound is loudest at the apex, are generally thought to be of no clinical significance. It is our purpose in this report to present the record of patient with such a rhythm, caused, apparently, by an aneurysm of the left ventricle. It should be mentioned that, when the gallop was perceived, we did not think that it was of any consequence. The investigation was carried out in the hope of being able to ascertain, with the use of modern instruments, the origin of the ectopic sound.

REPORT OF CASE

The patient, a 52-year-old colored man, was first seen May 14, 1938. He had been referred to us for an opinion as to whether arsenicals should be administered as a part of the treatment of his latent syphilis. At that time he had no symptoms of heart disease. His health had always been good, but he had acquired a urethral chancre in 1918. He was unable to recall having had any secondary manifestations of syphilis. In 1934, it was discovered that his blood Wassermann reaction was positive, and he received antisyphilitic treatment for two months. Early neurosyphilis then was diagnosed, and he was sent to a state hospital, where he remained for six months. During this time he was given sixteen ''fever'' treatments and sixteen injections each of a bismuth compound, a mercury compound, and neoarsphenamine. After he was discharged from this institution, he was in good health, and resumed his usual occupation as a porter in a railroad station. In February, 1938, the blood Wassermann and Kahn reactions were found to be positive, and he was advised to resume treatment.

On physical examination the patient was found to be a tall, spare, well-muscled, and apparently healthy, colored man. There were no skin lesions. His pupils were circular, equal, and reacted to light and in accommodation. There were no mucous patches or other lesions in the oral cavity. His teeth were in good condition. Examination of the anus, rectum, and external genitalia showed nothing abnormal. All of the deep tendon reflexes were present, and there was no Romberg sign. The lungs and the abdomen were normal. The accessible arteries were moderately thickened and somewhat tortuous. The apex impulse of the heart was seen and felt in the fifth intercostal space about 9 to 10 cm. to the left of the midsternal line. Percussion showed no enlargement of the heart or aorta. The blood pressure, in the sitting position, was 120/64 in both arms. The pulse rate at rest varied from 56 to 64 per minute. The heart tones at the base were distant, distinct, and apparently normal. The sounds at the apex attracted attention. There one heard a sharp tone almost midway between the first and the second heart sounds. Its intensity approximated that of the second sound. It could be heard from the apex

to the lower part of the left border of the sternum but was diminished in intensity in the latter region. Change in posture, exercise, and the Valsalva experiment had no influence on the quality or duration of the extra heart sound. Examination of the urine on several occasions revealed no abnormality. A teleroentgenogram which was made in June, 1938, revealed no enlargement of the heart but disclosed a prominent aortic "knuckle." Roentgenologically, the lungs and great vessels were normal. The shadow of the left ventricle, at that time, aroused no suspicion. Electrocardiograms were made on several occasions and were interpreted as showing normal mechanism, with infrequent extrasystoles of supraventricular origin.
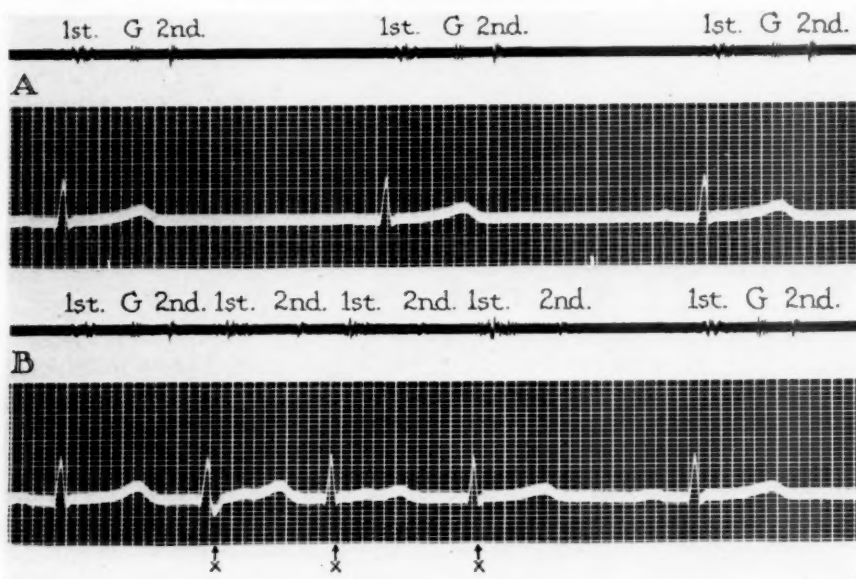

Fig. 1.—Simultaneous stethogram and electrocardiogram showing: A, Systolic gallop sound (G). B, Three successive supraventricular extrasystoles (X) which produced no gallop sound.

Further studies to ascertain the cause of the systolic gallop rhythm were then undertaken. Fluoroscopic examination of the heart disclosed a small (4 to 5 cm. long) aneurysm of the lateral wall of the left ventricle, with characteristic outpouching during ventricular systole. The other motions of the heart were normal. The aorta was seen to be elongated and moderately dilated, but the radioscopist, Dr. E. E. Barth, thought that aortic atherosclerosis, and not syphilitic aortitis, was responsible for this alteration. Simultaneous stethographic and electrocardiographic records fully confirmed our clinical impression that the gallop sound occurred between the first and second heart sounds. While one of the records was being taken, several consecutive extrasystoles of supraventricular origin occurred. During this time there was no gallop. Efforts to produce extrasystoles were unsuccessful. Electrocardiograms, jugular phlebograms, femoral arteriograms, digital (great toe) plethysmograms, and apex cardiograms were made simultaneously. Fortunately, on one occasion, when we were recording the arterial pulse, digital pulse volume, and electrocardiogram, an isolated extrasystole occurred. Finally, a roentgenkymogram was made while an electrocardiogram was being recorded. The results of these studies can be summarized briefly, as follows:

1. The stethographic record of the gallop sound consisted of four or five spikes which lasted 0.04 sec. The dominant frequency was 100 to 125 double vibrations

per second. In intensity and general appearance it was similar to the second heart sound. The gallop occurred 0.24 sec. after the onset of the QRS complex, 0.18 sec. after the commencement of the first sound, and 0.16 sec. before the beginning of the second sound. Thus, it was a true systolic gallop rhythm (Fig. 1).

2. Comparison of the jugular phlebogram, the electrocardiogram, and the stethogram revealed no right auricular activity that might account for the gallop (Fig. 2A).

3. Comparison of the stethogram with the apex cardiogram disclosed no motion of the chest wall which was simultaneous with the gallop. Thus, the extra heart sound was not caused by impact of the heart against the thoracic wall (Fig. 2B).
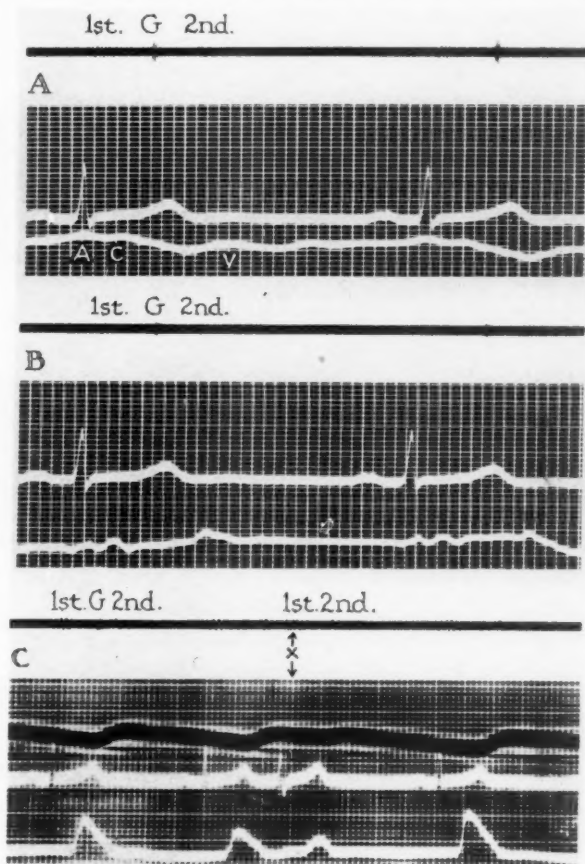

Fig. 2.—A, Simultaneous stethogram, electrocardiogram, and right jugular phlebogram. B, Simultaneous stethogram, electrocardiogram, and apex cardiogram. C, Simultaneous stethogram, digital plethysmogram, electrocardiogram, and femoral arteriogram, showing a hypodynamic supraventricular extrasystole (X).

4. Examination of the roentgenkymogram revealed typical paradoxical movement of the wall of the left ventricle, commencing 0.14 sec. after the onset of ventricular systole, when the heart rate was 60 per minute. The maximum outward motion of the aneurysm occurred 0.28 sec. after the onset of systole. The gallop occurred during this interval (Fig. 3).

5. The gallop also coincided with aortic filling, but the extra sound was heard very faintly over the aorta and could not possibly have been caused by the impact of the aorta against neighboring structures.

It was fairly apparent, therefore, that the gallop was in some way related to the outward motion of the aneurysm of the left ventricle. We made several assumptions in an attempt to explain the production of the gallop sound, as follows:

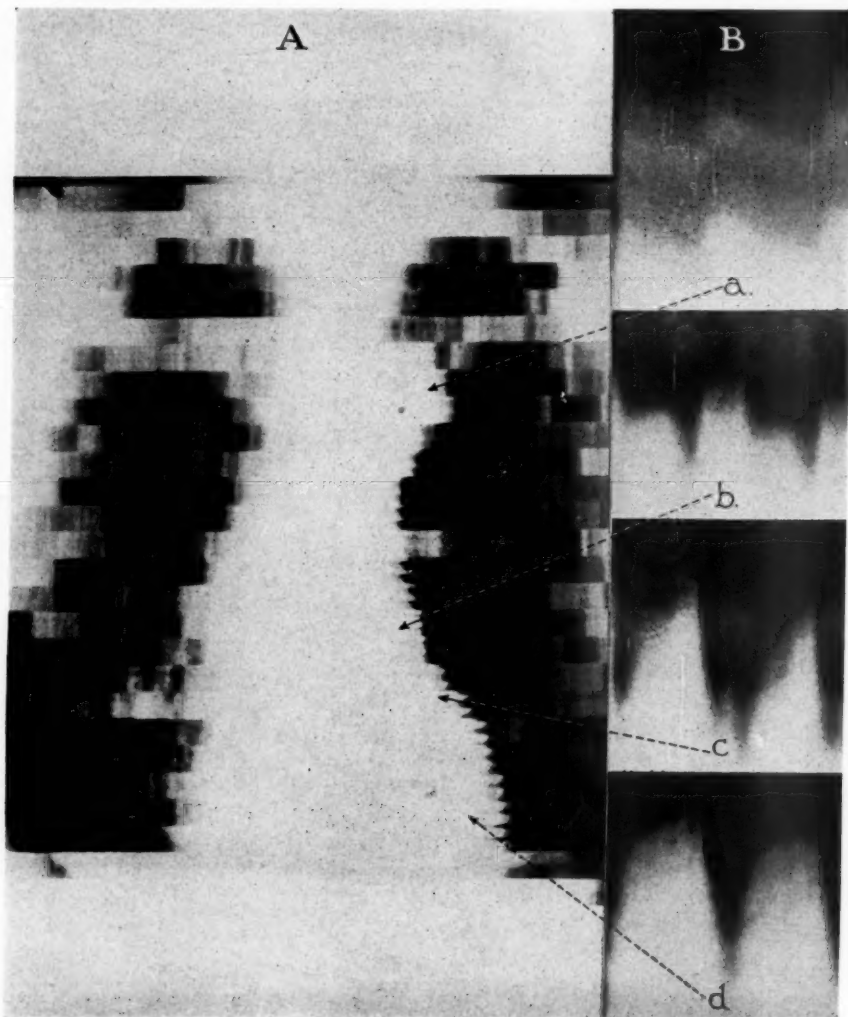1. The aneurysm was approximately at the site of the attachment of the anterior papillary muscle (upper part).

Fig. 3.—*A*, Roentgenkymogram, showing paradoxical movement of left ventricle (area *c*). *B*, Enlargements of areas from the border of the kymogram arranged to show simultaneous movements: *a*, aortic arch; *b*, left auricular appendage (or left auricle); *c*, left ventricular aneurysm; *d*, apex of left ventricle. Upward movement on the kymographic enlargements represents cardiac filling. Time relations from left to right.

2. The gallop occurred at a time in the cardiac cycle when the ventricle was almost empty, when intraventricular pressure was still very high, and when the papillary muscles were under great tension.

3. Towards the end of systole, when the aneurysm suddenly bulged outward, it carried with it the attachment of the anterior papillary muscle. This should have deformed the anterior leaflet of the mitral valve, permitting a sudden reflux of blood into the left auricle. The latter is quite possible, for left intraauricular pressure is much less than aortic pressure.

This idea, namely, that a deformity of the mitral valve, with a sudden reflux of blood into the left auricle, may cause gallop, gains support from two widely different observations, to wit:

1. As was noted previously, the gallop failed to occur when an extra-systole occurred (Fig. 1B); extrasystoles are hypodynamic. The simultaneously recorded femoral arteriogram, digital (great toe) plethysmogram, and electrocardiogram showed one premature beat of supraventricular origin, and it may be seen readily that the amplitude of the femoral and digital pulses was considerably less than usual (Fig. 2C). This observation suggests that, when the premature ventricular contraction occurred, the pressure in the left ventricle was less than usual, and we find no difficulty in assuming, further, that the ventricular pressure was not high enough to produce the distortion of the anterior mitral leaflet which is necessary for the production of the gallop.

2. Inspection of the roentgenkymographic silhouette of the left auricle (or of the left auricular appendage) disclosed a sudden, short, outward motion which was coincident with the maximum outward thrust of the aneurysm (Fig. 3). This extra peak is not seen in normal roentgenkymo-grams, and is, we believe, a result of the reflux of blood from the left ventricle into the left auricle.

In our opinion, the combination of direct and circumstantial evidence that has been presented is sufficient to explain the genesis of the gallop rhythm in this case. Systolic gallop rhythm is generally held to be purely incidental, but we believe that it may be a sign of aneurysm of the left ventricle.

CONCLUSIONS

1. In this case, a careful search for the cause of systolic gallop rhythm led to the discovery of an aneurysm of the left ventricle and suggested that such an aneurysm, by distorting the mitral valve during systole, may cause gallop rhythm.

2. In this case, at least, the systolic gallop rhythm at the apex was certainly a sign of a pathologic process, namely, aneurysm of the left ventricle.

303 E. CHICAGO AVENUE

Department of Reviews and Abstracts

Selected Abstracts

Wégria, René, and Wiggers, Carl J.: Factors Determining the Production of Ventricular Fibrillation by Direct Currents. (With a Note on Chronaxie.) Am. J. Physiol. **131**: 104, 1940.

This research was designed to establish, as far as possible, the conditions under which ventricular fibrillation is produced by direct currents of different durations and to offer a logical explanation for its occurrence. For this purpose D. C. shocks ranging from 1 to 50 Ma. were applied for intervals of 0.01 to 0.33 second to a small area of dogs' left ventricles by nonpolarizable electrodes. Shocks were introduced in alternating directions at every sixth ventricular beat and were so spaced that they fell progressively earlier or later in relation to normal cycles. In this way, the incidence of closing and opening as well as duration of action could be established. Our analysis leads to the following conclusions:

1. The dominant factor which determines the induction of ventricular fibrillation by an electrical stimulus is the fact that any type of stimulus above a certain critical value, introduced during the vulnerable period of late systole, causes simultaneously a premature contraction plus some local or generalized disturbance of conduction which permits irregular re-entry of impulses and leads to the various stages of fibrillation described by one of us.

In the case of direct currents, the effective excitant may be (a) a brief rectilinear shock, probably not more than 0.04 second in duration or (b) the closing or opening of more prolonged currents during this period of vulnerability.

In the case of D. C. stimuli which exceed 0.05 or 0.06 second, several secondary factors may enter which also lead to fibrillation.

The factor which determines fibrillation in any specific instance depends upon the duration of the D. C. stimulus, upon the time that closure occurs with respect to the cycle, upon the character of the premature response evoked, upon the relation of opening to a normal or premature beat, etc. However, we believe that it can be demonstrated in many of these highly variable conditions, and is probable in others which cannot be so definitely analyzed, that a second effective stimulus, artificial or physiologic, must strike during the vulnerable period of a premature systole in order to cause fibrillation. Such a concept harmonizes the apparent discrepancy that brief shocks of any form only cause fibrillation when they are applied during the vulnerable period, whereas D. C. shocks longer than 0.05 second may do so, when they fall entirely in diastole, partly in systole and partly in diastole, or even when they extend over several beats.

The chief secondary mechanisms by which shocks longer than 0.05 or 0.06 second become more potent fibrillation stimuli, are fundamentally due to two well-known peculiarities of such shocks: 1. They are no longer unitary stimuli but are capable of exerting separate C and O effects, and 2, they cause effects (electrotonic?) during persistence of the current, which give rise to unpredictable spontaneous impulses either during the flow of the current or shortly after its cessation.

The manner in which such secondary phenomena lead to fibrillation with currents of increasing duration (0.07-0.33 sec.) is graphically depicted in Fig. 2. In a broad way, these conditions can be resummarized verbally as follows:

(A) When C, falling during the vulnerable phase or early diastole, causes a premature contraction of such duration that O of effective strength occurs during its vulnerable period.

(B) When C occurs during the refractory period of a normal cycle, but the continued passage of the current causes a spontaneous premature beat in the next or any subsequent diastole and O occurs during its vulnerable period.

(C) When C occurs during the refractory period of a normal cycle and O falls during early diastole of this or any subsequent beat causing a premature contraction and later a spontaneous premature impulse which coincides with the vulnerable period of the first premature beat due to O.

In view of (a) the greater tendency even of weak currents, 0.24-0.33 second in duration, to evoke spontaneous premature beats not related to C or O; (b) the frequency of fibrillation by such currents in our series and (c) the nonexistence in the beating heart of any span of iso-excitability, the determination of chronaxie of the ventricles by use of direct currents introduces difficulties.

AUTHORS.

Wégria, René, and Wiggers, Carl J.: Production of Ventricular Fibrillation by Alternating Currents. Am. J. Physiol. **131:** 119, 1940.

The effects of 60 cycle alternating currents applied locally to the dog's left ventricle through nonpolarizable electrodes are analyzed:

A. C. stimuli composed of ½ to 4 waves (0.008-0.0666 sec.), like brief D. C. shocks, act as a unitary stimulus. When they start or fall entirely within the vulnerable period, they always give a response if strong enough; that response is one or two premature ventricular systoles followed or not by ventricular fibrillation. The influence of the moment of onset or phase angle in relation to the vulnerable period has not been established. A similar stimulus during the refractory period is ineffective. When given during diastole, it causes one premature beat and never produces fibrillation.

Stimuli composed of more sine waves (generally 7 to 9) produce no effect or an occasional premature beat when they are very weak. A similar number, of moderate strength, falling entirely in the refractory phase are ineffective; but when they encroach upon, cover, or start in the vulnerable period, they evoke a single premature contraction, but never cause fibrillation. If they start ever so early in diastole, however, fibrillation occurs. Strong currents also cause fibrillation when they enter during the vulnerable period.

The occurrence of fibrillation by early diastolic shocks, incapable of acting during the vulnerable period, can be explained by the fact that an effective portion of the series now falls during the vulnerable of a premature beat. In other words, an apparent diastolic fibrillation is actually a fibrillation started during the systolic vulnerable period of a premature beat.

A. C. stimuli, with durations varying from 0.2 to 1 second or more, promptly cause fibrillation when currents are of moderate or great strength. However, even very weak currents (0.5 to 1.0 Ma.) cause ventricular tachycardia which may revert to a normal rhythm after removal of the stimulus or may eventuate in fibrillation either while the A. C. is operating or shortly after its withdrawal.

An analysis of the ventricular tachycardia reveals that the rhythm is not quite regular and that a tendency to progressive increase in rate occurs. In some instances, electrical alternation exists and a peculiar dissociation of electrical and left

ventricular pressure occurs in alternate beats, despite the fact that electrodes are applied to the left ventricle. Therefore, the probability is weighed that the tachycardia is caused by re-entry rather than by periodic focal stimuli. However, conclusive evidence for such a theory is not adduced.

The reason why weak alternating currents produce fibrillation in some tests and not in others remains obscure. However, definite evidence is presented that the duration of such currents is not a factor provided this exceeds 0.2 sec. The mechanisms through which fibrillation eventuates during or shortly after use of such weak A. C. currents are difficult to analyze on the basis of evidence so far available.

AUTHORS.

Schroeder, Henry A., and Steele, J. Murray: The Behavior of Renal Blood Flow After Partial Constriction of the Renal Artery. J. Exper. Med. 72: 707, 1940.

Studies have been made of the behavior of renal blood flow after partial constriction of the renal artery in twenty-four dogs.

When reduction in renal blood flow is produced by partial constriction of the renal artery, a readjustment of flow in the direction of normal occurs within a few minutes, subsequent constriction being again followed by a return of flow toward normal until the artery is markedly constricted.

Renal blood flow after marked constriction of the artery becomes extremely susceptible to the vasoconstrictive action of small doses of adrenalin, and flow may cease with larger doses for a considerable period of time.

Arterial hypertension of significant degree may follow partial constriction of one renal artery during brief experiments when adrenalin in addition has been administered.

Further evidence is presented in favor of the concept that the renal circulation enjoys a control independent of systemic arterial pressure.

AUTHORS.

Squire, J. R.: An Instrument for Measuring the Quantity of Blood and Its Degree of Oxygenation in the Web of the Hand. Clin. Sc. 4: 331, 1940.

An instrument is described by which the light transmission through the web of the hand is measured at two different spectral regions. From this, the quantity of blood present and its degree of oxygenation are calculated. The apparatus is portable and suitable for clinical investigations.

AUTHOR.

Steincrohn, Peter J.: A New Observation Helpful in the Diagnosis of Coronary Thrombosis. Ann. Int. Med. 14: 495, 1940.

Descriptions of coronary thrombosis pain in the literature do not mention or stress the importance of evaluating the quality of this pain.

The outstanding characteristic of this pain is its rhythm and periodicity.

The patient must be observed carefully before the presence of these characteristics can be determined.

If the periodicity of these pains is observed, the diagnosis can be made and will be substantiated later by positive evidence.

An analysis of six patients has been made to describe this pain syndrome.

AUTHOR.

Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals. Public Health Reports 55: 1599, 1940.

During the five-year period from January 1, 1930, to December 31, 1934, there were 5,921 admissions involving rheumatic heart disease, rheumatic fever, Syden-

ham's chorea, and subacute bacterial endocarditis to thirty-six hospitals in Philadelphia. Of these admissions, 5,801 were for rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis on a rheumatic basis, while 120 were for subacute bacterial endocarditis in which a definite relationship to rheumatic heart disease was not determined.

Comment is made on difficulties in terminology in describing rheumatic conditions, and on the variety of combinations in which they occur. Considerable improvement in diagnostic standards and in the maintenance of hospital records was noted during the period under study.

The diseases under study were indicated in 0.70 per cent of admissions from all causes to Philadelphia hospitals. In three children's hospitals they were present in 1.56 per cent of all admissions. In fourteen teaching hospitals these conditions were noted in 0.79 per cent of all admissions. Most of the admissions were to the large general and children's hospitals located in the center of the city.

It is estimated that the conditions under study were present in 2.4 per cent of medical admissions to general hospitals and 5.8 per cent of medical admissions to children's hospitals.

Rheumatic heart disease, rheumatic fever, and Sydenham's choreas were the principal causes of 87.2 per cent of these admissions, while subacute bacterial endocarditis was the principal cause of 5.8 per cent of the 5,921 admissions constituting this series. Practically all admissions involving rheumatic fever and chorea were caused primarily by those conditions.

Over 93 per cent of admissions involving rheumatic conditions were to the wards of general and children's hospitals. This substantiates the view that rheumatic heart disease is essentially a problem of the class of patients treated on hospital wards.

The total number of admissions to Philadelphia hospitals for rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis, most of which is superimposed on rheumatic heart disease, is probably slightly over 1,200 a year; of these, over 900 are first admission.

It is estimated that rheumatic conditions and subacute bacterial endocarditis were factors in 272,000 patient-days in Philadelphia hospitals during this five-year period. Of this number, only about 5,000 patient-days were due to subacute bacterial endocarditis not superimposed on rheumatic heart disease. It is estimated that rheumatic conditions were in varying degrees accountable for 187,000 patient-days in general hospitals and 23,700 patient-days in children's hospitals. They result in over 40,000 patient-days annually in general and children's hospitals. In addition, there were about 61,300 patient-days caused by rheumatic conditions at the Children's Heart Hospital, a sanitarium furnishing prolonged convalescent care. Including this institution, rheumatic conditions account for, or at least are concerned in, over 50,000 patient-days each year in Philadelphia hospitals.

It is estimated that the conditions under study accounted for or were responsible factors in 2.0 per cent of patient-days in general and 7.5 per cent in children's hospitals.

The estimated cost of hospitalization of patients with these conditions is over $272,000 a year, exclusive of physicians' services, most of which are rendered gratuitously.

Prolonged convalescent care is furnished such a small percentage of patients with rheumatic fever, chorea, and rheumatic heart disease that it is not possible to evaluate its benefit. Of the fatal cases under 20 years of age, only 13.6 per cent had been admitted to that institution.

AUTHOR.

Hedley, O. F.: **Rheumatic Heart Disease in Philadelphia Hospitals. II. Age, Race, and Sex Distribution and Interrelation of Rheumatic Fever, Sydenham's Chorea, Rheumatic Heart Disease, and Subacute Bacterial Endocarditis.** Public Health Reports 55: 1647, 1940.

An analysis has been made of the age, race, and sex distribution of rheumatic fever, Sydenham's chorea and rheumatic heart disease in Philadelphia hospitals from January 1, 1930, to December 31, 1934, based on the age at initial admission during the period under study and the age at onset as indicated in the clinical histories. In some cases the onset occurred during stay in hospital; in other instances it was determined by review of patients' past histories. Figures have been prepared showing the age distribution and cumulative percentages by five-year age periods of a number of important rheumatic manifestations.

The literature has been reviewed and tables prepared showing the association of rheumatic fever and clinical manifestations of rheumatic heart disease, the age at onset of rheumatic infections, the percentage of Sydenham's chorea presenting clinical evidence of rheumatic heart disease, the percentage of rheumatic heart disease with histories of rheumatic fever and Sydenham's chorea, and the percentage of subacute bacterial endocarditis superimposed on rheumatic heart disease.

The importance of rheumatic heart disease as a problem of childhood and youth is emphasized by the fact that the onset of 76.4 per cent of rheumatic fever, 98.2 per cent of chorea, and 69.1 per cent of rheumatic heart disease occurred before age 20. The mode of the age of onset of rheumatic fever was 8.7 years, of Sydenham's chorea 9.3 years, and of rheumatic heart disease 8.9 years. Of the initial admissions during the period under study (not necessarily the first admissions for these conditions), 59.6 per cent of rheumatic heart disease occurred among persons under 20 years of age. Despite the fact that this is the first study on a large scale of the major rheumatic manifestations at all ages, the peak of onset of rheumatic fever, Sydenham's chorea and rheumatic heart disease occurred in the 5 to 9 year age period.

The expression "juvenile rheumatism" is regarded as an inappropriate description of a disease which begins for the most part during childhood, but is characterized by chronicity, exacerbations, and recurrences throughout adult life. Although essentially a problem of childhood, and youth, attacks of rheumatic fever may occur at almost any age.

In only 2.7 per cent of cases of rheumatic fever and 5.7 per cent of cases of rheumatic heart disease did the onset occur after age 40. Rheumatic heart disease is decidedly infrequent among hospital patients over 60 years of age. Unlike many other types of heart disease, rheumatic heart disease is not a problem of great importance among persons past middle age.

Rheumatic fever, Sydenham's chorea and rheumatic heart disease are relatively uncommon under 5 years of age. Very few cases of rheumatic fever under age 2 were admitted, and comparatively few previous histories indicated the onset of rheumatic infection in infancy.

Approximately the same number of males as females were admitted for rheumatic fever; slightly more females than males gave histories of rheumatic fever. The distribution of rheumatic heart disease according to sex indicated a slightly greater percentage of females. Sydenham's chorea was nearly twice as common among females.

Rheumatic fever and rheumatic heart disease were less common among negroes than might be expected, considering their unfavorable economic circumstances as a result of which they are more likely to be hospitalized. A considerably greater **percentage of first** attacks of rheumatic fever was indicated among colored persons

in the 20 to 39 year age period. Sydenham's chorea was relatively uncommon among negroes. The possibility is suggested that rheumatic heart disease is more likely to develop in association with chorea among colored persons.

The clinical records of 63.3 per cent of 1,324 cases of rheumatic fever indicated diagnoses of rheumatic heart disease. The percentage of rheumatic fever with heart disease was greatest among persons under 20 years of age.

Of the 3,654 cases of rheumatic heart disease, 61.5 per cent gave histories or exhibited clinical manifestations of rheumatic fever. Sydenham's chorea, with or without rheumatic fever, was indicated in 15.2 per cent of rheumatic heart disease. Excluding the cases of chorea which also gave histories or presented clinical evidence of rheumatic fever, 11.4 per cent of the cases of rheumatic heart disease gave histories of having had chorea without frank attacks of rheumatic fever. Altogether, 72.7 per cent of rheumatic heart disease gave histories or exhibited clinical manifestations of rheumatic fever, Sydenham's chorea or both of these conditions.

Diagnoses of rheumatic heart disease were indicated in 42.1 per cent of Sydenham's chorea. This percentage would probably have been higher had these cases been followed after discharge from hospital. These studies and the results of a number of other investigations indicate that a child with almost any form of Sydenham's chorea stands a much greater chance of developing rheumatic heart disease than a child who has never had any form of Sydenham's chorea. This, together with the fact that 10 to 15 per cent of cases of rheumatic heart disease give histories of chorea, many without frank attacks of rheumatic fever, suggests that Sydenham's chorea should continue to be regarded as a manifestation of the rheumatic state.

The importance of activity of rheumatic infection is suggested by the fact that 56.4 per cent of 3,446 cases of rheumatic heart disease uncomplicated by subacute bacterial endocarditis were regarded as presenting signs of rheumatic activity. This is probably an underestimate. Over 80 per cent of cases under age 20 were considered as having active rheumatic infection. Of the 3,654 cases of rheumatic heart disease, including subacute bacterial endocarditis when occurring as a complication, 22.9 per cent presented clinical manifestations of rheumatic arthritis. The percentage of rheumatic heart disease with rheumatic fever was greater among cases under 20 years of age.

Among 324 cases of subacute bacterial endocarditis, 64.5 per cent were regarded as superimposed on rheumatic heart disease. Comment is made on the infrequency of subacute bacterial endocarditis as a complication of cardiovascular syphilis.

Comment is made upon the discrepancy in the age distribution of clinical diagnoses of rheumatic fever in hospitals, most of which are either approved for internship by the American Medical Association or are accredited children's hospitals, and the age distribution of deaths attributed by physicians to rheumatic fever, as indicated by mortality statistics obtained from the local office of vital statistics. This suggests the inadvisability of making rheumatic fever at all ages a notifiable disease. Measures directed toward combating this problem should be concentrated on persons under 20 years of age, the period in which most cases develop.

AUTHOR.

Swift, Homer F.: Rheumatic Heart Disease. Pathogenesis and Etiology in Their Relations to Therapy and Prophylaxis. Medicine 19: 417, 1940.

An attempt is made to describe the manner in which cardiac and vascular damage develop as a result of rheumatic fever, and how the final picture results from either repeated insults to important tissues or from a long-continued low grade inflammatory process. Attention is directed toward the importance of functional trauma in localizing the permanent damage and scarring to certain

structures, and to the role of this functional trauma in helping to continue an inflammatory process which might subside rapidly were complete rest attainable; as a corollary, prolonged physiologic rest is indicated to keep scarring at the minimum. The factor of infection in rheumatic fever is apparently closely related to the action of group A hemolytic streptococci; hence an important element in prevention of relapses is protection from such streptococci. A consideration of these factors is necessary either in handling a rheumatic individual or in framing a larger general program. Elsewhere are presented other features of rheumatic fever, such as the probable size of the problem and environmental influences which are amenable to alteration.

AUTHOR.

Stone, Simon: Treatment of Sydenham's Chorea by Fever and Vitamin B Therapy. New England J. Med. 223: 489, 1940.

Twenty patients with severe, moderately severe, and mild cases of Sydenham's chorea were treated. Five of the seven severe cases received artificial fever therapy, together with vitamin B complex given orally and thiamin chloride given parenterally. One severe and one moderately severe case received thiamin chloride parenterally and vitamin B complex orally, while all the others received oral medication only.

In the electropyrexia-treated cases recovery was produced with about fourteen hours of fever at 104° F. or over. When this was combined with vitamin B therapy, advanced cardiac conditions were found to be no contraindication to the fever treatment. Usually a change for the better in the carditis was noted at the end of the treatment.

One of the two cases treated with thiamin chloride responded with cessation of symptoms after the second intravenous injection of 10 mg. of the drug.

Various degrees of behavior disturbances were seen in most of the moderately severe and milder cases. They all received 4 to 8 c.c. of vitamin B complex orally, three times daily. The improvement in physical manifestations was less rapid than it was in the fever-treated cases, but most of the symptoms disappeared within one month. No hospitalization was required for any patients in this group. Improvement was noted in their behavior concomitantly with the change for the better in choreic manifestations.

AUTHOR.

Perry, C. Bruce: Rheumatic Heart Disease in Identical Twins. Arch. Dis. Childhood. 15: 177, 1940.

Two pairs of apparently identical twins are described. In the first both children suffered a similar rheumatic attack following a sore throat, which in only one produced scarlet fever. In the second, only one child developed acute rheumatism and carditis although they had been brought up together. It is concluded that while heredity is of considerable importance in the causation of acute rheumatism, another factor, probably infection, plays an equally, if not more, important role.

AUTHOR.

Prinzmetal, Myron, Lewis, Harvey A., and Leo, Sidney D.: The Etiology of Hypertension Due to Complete Renal Ischemia. Clin. Sc. 72: 763, 1940.

Perfusates of totally ischemic kidneys of cats contain a pressor substance which is not present in the perfusates of normal kidneys, ischemic hind limbs, or ischemic gravid uteri.

The pressor material in ischemic renal perfusates originates directly in the kidney as a result of complete ischemia.

The pressor principle contained in ischemic renal perfusates is the cause of the hypertension which follows the re-establishment of circulation in completely ischemic kidneys, since perfusates of unreleased completely ischemic kidneys contain more pressor material than perfusates of released ischemic kidneys of the same animal.

The pressor principle in ischemic renal perfusates is presumed to be renin for the following reasons: a) Both substances are destroyed by boiling. b) Both substances induce tachyphylaxis. c) The configuration of both pressor curves is identical. d) The pressor action of both is not reversed by 933F, proving they are not epinephrine-like substances. e) When incubated with plasma, both form a heat-stable pressor substance. f) The pressor effect of both is uninfluenced by a previous injection of cocaine. g) Unreleased, completely ischemic kidneys yield more pressor material on extraction than do released ischemic kidneys of the same animal.

The perfusates of blood-free ischemic kidneys contain more renin than those of blood-filled ischemic kidneys.

A method is described by which the power of various substances to inhibit or enhance the production of renin in the ischemic kidney may be tested.

A small amount of the heat-stable pressor substance, presumably angiotonin or hypertensin, is formed by the reaction of the pressor material (renin) and plasma in the vessels of the kidney during the period of complete ischemia.

AUTHORS.

Muñoz, J. M., Braun-Menéndez, E., Fasciolo, J., and LeLoir, L. F.: The Mechanism of Renal Hypertension. Am. J. M. Sc. 200: 608, 1940.

The ischemic kidney secretes renin. This substance is an enzyme which acts on a blood globulin ("hypertensin precursor") and gives rise to a substance ("hypertensin") which has a direct vasoconstrictor action. Another enzyme, "hypertensinase," which destroys hypertensin is present in blood and tissues.

Hypertensin has been found in the blood of ischemic kidneys and can also be prepared in vitro by incubating renin with blood globulins. Some chemical and pharmacologic properties of hypertensin have been studied.

Methods are described for the estimation of renin, hypertensin precursor, and hypertensinase in blood.

After injection of renin into chloralosed dogs, the hypertensin precursor decreases and even disappears from the blood. After nephrectomy, the hypertensin precursor increases and hypertensinase decreases. AUTHORS.

Simon, Morris A.: The Nephrotic Syndrome With Hypertension in Diabetes Mellitus. Canad. M. A. J. 43: 425, 1940.

In older patients with diabetes of long standing, a nephrotic syndrome (massive edema of nephrotic distribution, hypoproteinemia, hypoalbuminemia, lowering of the albumin-globulin ratio, and massive albuminuria) may supervene, which is accompanied by hypertension and a variable degree of renal failure.

The kidneys of such persons show a characteristic and distinctive glomerular and arteriolar degenerative change which indicates that one is dealing with a distinct clinicopathologic entity.

Two cases which fulfill the clinical and pathologic criteria of this disease entity have been reported. AUTHOR.

Fischer, Robert: Clinical Investigation Concerning the Jugular Venous Pulse. Cardiologia 4: 267, 1940.

The c-waves of the jugular vein pulse tracing are bigger in auricular fibrillation than in normal rhythm; the systolic decrease disappears if cardiac congestion develops. Typical changes of the jugular pulse can be observed in cases of tri-

cuspidal insufficiency with auricular fibrillation. The jugular vein pulse does not show typical changes in any other valvular disease; however, it reveals conditions of cardiac failure and of the venous side of the peripheral circulation.

AUTHOR.

Parsons, Leonard G., and Ebbs, J. H.: Generalized Angiomatosis Presenting the Clinical Characteristics of Storage Reticulosis. Arch. Dis. Childhood. **15:** 129, 1940.

A clinical and pathologic report is given of a 14-year-old girl who showed clinical evidence of the ''osseous form of Gaucher's disease'' but who at post-mortem examination was found to have suffered from cavernous angiomata varying in size in the liver, spleen, retroperitoneal glands, thymus, mediastinum, lungs, pleura, kidneys and most of the bones of the body. The case is a difficult one to classify because of the widespread involvement of reticuloendothelial tissue, although histologically it is apparently an example of multiple hemangiomata, the cells of which have benign histologic characters. A discussion of the relation of this condition to ''reticulosi'' and ''reticuloendotheliosis'' is included.

AUTHORS.

Grant, R. T.: Observations on Periarteritis Nodosa. Clin. Sc. **4:** 244, 1940.

A series of seven cases of periarteritis nodosa is described.

The chief pathologic and clinical features of the disease are discussed.

The evidence suggests that periarteritis nodosa is much less rare than is commonly thought, that it is not necessarily or even usually fatal, and that it can be recognized at the bedside in a considerable proportion of cases.

AUTHOR.

Smith, Fred M.: Concerning the Correlation of the Pathology and Symptoms of Coronary Artery Disease. Ann. Int. Med. **14:** 65, 1940.

In coronary artery disease the changes in the arteries are the only constant feature. The response of the heart in any particular instance is no doubt influenced by many factors, but the ability to maintain an adequate circulation to the myocardium through the development of collateral circulation is perhaps the most important. Clinical and experimental studies have demonstrated that this is more effectively accomplished if there is a gradual occlusion of the vessels. In the normal subject the communications between adjacent vessels are limited and in most instances are made by means of the smaller vessels. Therefore, the abrupt closure of one of the main vessels early in the course of the disease usually results in a large area of infarction. If, on the other hand, the obstructive process develops slowly and is not terminated too soon by a thrombus, there may be very little or perhaps no significant degeneration of the myocardium. Thus, the rate of the formation of the obstruction determines in a large measure the extent of the collateral circulation, the histologic changes in the myocardium, the efficiency of the heart, and quite probably the character of the clinical expression.

Of the various symptoms pain is the most difficult to explain. Most workers in this field believe that insufficiency in the coronary circulation is the basic factor. Two features in particular, however, are difficult to explain on this hypothesis. In the first place, there is an occasional case in which there is no demonstrable disease of the coronary arteries or in which, if disease is present, it is regarded as insignificant. Moreover, many with advanced disease of the coronary arteries never have angina pectoris. In the former the angina is usually associated with conditions which

impose excessive demands on the heart. There is also the possibility that increased vasomotor tone or spasm may be a factor. Finally, in the cases of extensive disease of the coronary arteries, the receptive state of the sensory nerve endings, or perhaps of the nervous mechanism in general, may determine the presence or absence of pain.

AUTHOR.

Carere-Comes, O., and Canna, S.: The Musculature of the Veins at Varying Ages. Quantitative Histological Research. Cardiologia 4: 283, 1940.

Using a quantitative-histologic method, the authors have examined morphologically and quantitatively the senile variations in the muscle of the walls of various veins (femoralis, saphena magna, omeralis, mediana basilica, jugularis interna, cava inferior) of each of thirty-eight corpses.

The structural and quantitative similarities and differences in the vein muscle in relation to the regions explored are described.

The changes in the various muscle sheaths due to old age, together with the appearance of the senile atrophy of the vein muscle, are noted.

The sex difference in the vein muscle is pointed out.

The possible functional importance of the place variations and senile changes in the veins, the clearly functional relations between skeleton and vein muscle, and the similarity of the changes in the vein muscle with those changes in tonus and the venous pressure described by other authors are considered.

AUTHORS.

Asmussen, Erling, Christensen, E. Hohwü, and Nielsen, Marius: The Regulation of Circulation in Different Postures. Surgery 8: 604, 1940.

Our experiments indicate that the circulation rate in quiet standing is on the lower limit of which is really desirable and that, even if the fast pulse rate in the standing position in itself is no sign of insufficiency, it indicates on the other hand that some extra stress is put onto the pressure-regulating mechanism.

A diminished cardiac output during quiet standing has to be looked upon as a sign of insufficiency, even if the O_2 consumption and the arterial blood pressure remain normal. The vessels of the lower extremities are distended by hydrostatic forces; a large amount of blood remains there and consequently the filling and pressure of the central veins get too low to secure an adequate filling of the heart and a normal cardiac output. Through an increased heart rate and through compensatory contractions of the vessels in certain organs (e.g., in the intestines) a normal arterial blood pressure might be obtained. However, it must be remembered that a diminished circulation rate to these organs with partly contracted vessels locally may have an unfavorable effect. It may be of great importance that circulatory insufficiency due to a peripheral dilation of the vessels or to a loss of blood can be counteracted by an elevation of the lower extremities. The auto-transfusion of blood that can be made in this way may be of great significance. In cases where a circulatory insufficiency due to a disproportion between the total blood volume and the capacity of the vessels is obvious, any posture where hydrostatic forces can induce an increased filling of the vessels of the lower extremities should be avoided. Even a small decrease in cardiac output may mean a rather severe insufficiency of the circulation of certain organs. The beneficial effect of the reclining position to a great extent may be due to the abundant blood supply to the different organs obtainable in that position.

AUTHORS.

White, Paul D.: Pulmonary Embolism and Heart Disease. A Review of 20 Years Experience. Am. J. Med. Sc. 200: 577, 1940.

Pulmonary embolism has failed surprisingly to attract the interest and attention it has deserved from general practitioners and those working primarily in the field of internal medicine, in contrast to its long-standing recognition by surgeons and obstetricians as a serious complication after operation, accident, or childbirth. It needs emphasis as a medical disease because of its frequency and importance in nonsurgical and nonobstetric cases.

About one-third of the cases studied simulated heart disease and the remainder complicated it. Of the former (28 in number), one-half (14) showed the signs of acute cor pulmonale, including characteristic electrocardiographic abnormalities. In most cases pulmonary embolism is either so mild or so rapidly fatal that such signs are not present or the patients are examined only after the height of the effect of the pulmonary arterial obstruction has passed.

Pulmonary embolism and infarction are easily overlooked, especially in the presence of congestive heart failure, when they are most common; or they are erroneously diagnosed as something else, especially pneumonia, congestive heart failure, or coronary thrombosis.

Clues to the diagnosis lie in the occurrence of unexplained fever, leucocytosis, tachycardia, faintness, prostration, dyspnea, or even jaundice (from hemolysis of the infarct plus an engorged liver), especially in a cardiac patient with heart disease (and particularly in the presence of mitral stenosis or heart failure).

AUTHOR.

Allan, Warde B., and McCracken, Joseph P.: Aneurysm of the Pulmonary Arteries. Am. J. Syph., Gonor. & Ven. Dis. 24: 563, 1940.

Two cases of aneurysm of the pulmonary artery due to syphilis are reported, one of which is established; the findings in the second case are suggestive. The significant features are summarized, but no definite criteria for recognizing this condition are evident.

AUTHORS.

Nichols, Charles F., Ostrum, Herman W., and Widmann, Bernard P.: Aneurysms of the Ascending Aorta, Aortic Arch and Innominate Artery. A Clinical, Anatomical and Roentgenological Study. Am. J. Roentgenol. 43: 845, 1940.

Many articles dealing with aneurysms have been published but only a very limited number have been accompanied by anatomic studies. We have attempted in this presentation to emphasize the anatomic relation of the aorta and to show how a knowledge of this, as detailed in the accompanying illustrations, may serve to clarify and simplify the subject. Not only will this detailed anatomic relation be valuable in the diagnosis of aneurysms but it will also greatly aid in a differential diagnosis of all space-taking lesions which occur in the thorax, adjacent to the heart.

AUTHORS.

Brown, Samuel, McCarthy, J. E., and Fine, Archie: Cardiovascular Dynamics. Radiology 35: 290, 1940.

The historical development of roentgenkymography is briefly reviewed. The principle and technique are described. The physiologic processes related to movement of the cardiovascular dynamics under normal and abnormal conditions are discussed in more or less detail. It is concluded that roentgenkymography provides a perma-

nent record of roentgenoscopic observation. It is rarely of direct aid in diagnosis, but helps confirm the roentgenoscopic and roentgenographic findings.

AUTHORS.

Levin, Elias: Action of Coramine on Blood Volume in Cardiac Compensation and Decompensation. Rev. argent. de cardiol. 7: 146, 1940.

The circulating blood volume was determined in seven cardiac patients before and after intravenous injections of coramine. Three of the four compensated cardiac patients showed no change, while those with cardiac decompensation showed a reduction in blood volume. Only two patients, one decompensated and another compensated, reacted to the injection of coramine with an increase in blood volume, but in both cases the initial volume was smaller than normal.

Basing his conclusion on these results, the author concludes that the action of coramine depends on the existent circulatory blood volume; if it is increased, coramine will reduce it, and vice versa.

The mechanisms of these actions are probably different; while the increase of blood volume is mediated through peripheral vascular mechanism, its decrease is probably due to cardiac action.

AUTHOR.

Stroud, William D., and Twaddle, Paul H.: Observations Upon the Effect of Coramine in Certain Cardiac States. Ann. Int. Med. 14: 361, 1940.

It has been demonstrated that coramine may have a beneficial action on the abnormal respirations associated with cardiac disease. Dramatic responses, however, are not usually found from oral doses, but rather a slow progressive improvement—usually one to three days elapse before the optimum benefit is realized. A more prompt but transient response follows its use intravenously and may be attended (as used in 5 c.c. doses) by symptoms from widespread cerebral stimulation.

Cardiac efficiency was not shown to be constantly improved from prolonged oral use of coramine.

Decline in intrathecal pressure, following its intravenous administration, was observed and, to a less constant or striking degree, a decline in venous pressure. That these pressure changes are directly related to the improvement noted is considered doubtful. The present evidence points to coramine's stimulation, as a chemical agent, of the respiratory receptors, either peripherally or centrally.

Further studies are indicated.

AUTHORS.

Allen, C. R., Stutzman, J. W., and Meek, W. J.: The Production of Ventricular Tachycardia by Adrenalin in Cyclopropane Anesthesia. Anesthesiology 1: 158, 1940.

At least one action of cyclopropane is to render the dog's heart more irritable to adrenalin by direct stimulation of a brain center above the pons which sends impulses to the heart by way of the sympathetic nerves. The direct action of adrenalin on the heart thus sensitized produces ventricular tachycardia.

AUTHORS.

American Heart Association, Inc.

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

Executive Committee.